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⑪ Publication number: **0 417 721 A2**

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# EUROPEAN PATENT APPLICATION

⑲ Application number: **90117461.5**

⑤① Int. Cl.<sup>5</sup>: **C07K 5/10, C07K 5/08**

⑳ Date of filing: **11.09.90**

③① Priority: **11.09.89 US 405491**

④③ Date of publication of application:  
**20.03.91 Bulletin 91/12**

⑥④ Designated Contracting States:  
**AT BE CH DE DK ES FR GB GR IT LI LU NL SE**

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⑤④ **Novel peptidase and isomerase inhibitors.**

⑤⑦ This invention relates to activated electrophilic ketone analogs of certain peptidase substrates which are useful in inhibiting serine-, carboxylic acid- and metallo- proteolytic enzymes, the inhibition of which will have useful physiological consequences in a variety of disease states.

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## NOVEL PEPTIDASE AND ISOMERASE INHIBITORS

This invention relates to protease enzyme inhibitors useful for a variety of physiological end-use applications.

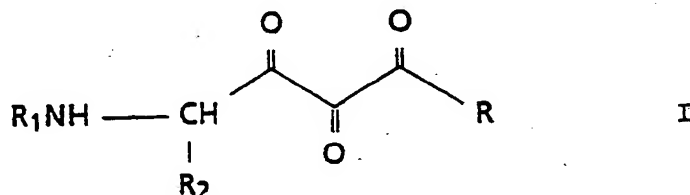
In its broad aspects, this invention relates to analogs of peptidase substrates in which the terminal carboxy group has been replaced by a tricarbonyl  $(-C(O)C(O)C(O)R)$  group. These peptidase substrate analogs provide specific enzyme inhibitors for a variety of proteases, the inhibition of which exert valuable pharmacological activities and therefore have useful physiological consequences in a variety of disease states.

In its more specific aspects, this invention relates to triketocarbonyl analogs of certain peptidase substrates which are useful in inhibiting serine-, carboxylic acid-, thiol-, and metallo-proteinases, the inhibition of which will have useful physiological consequences in a variety of disease states.

Still more specifically, this invention relates to tri keto analogs of peptidase substrates which fall within the following generic groupings characterized according to their active site dependencies. Such generic groupings are:

- I. Serine Proteinases: These include such enzymes such as Elastase (human leukocyte), Cathepsin G, Thrombin, plasmin, C-1 Esterase, C-3 Convertase, Urokinase, Plasminogen Activator, Acrosin,  $\beta$ -Lactamase; D-Alanine-D-Alanine Carboxypeptidase, Chymotrypsin, Trypsin and Kallikreins.
- II. Carboxylic Acid Proteinases: These include such specific enzymes as Renin, Pepsin and Cathepsin D.
- III. Metallo Proteinases: These include Angiotensin Converting Enzyme, Enkephalinase, Pseudomonas Elastase and Leucine Aminopeptidase.
- IV. Thiol Proteinases: Cathepsin B and Calpain.

The contemplated peptidase inhibitors of the foregoing enzymes are selected from the generic formula



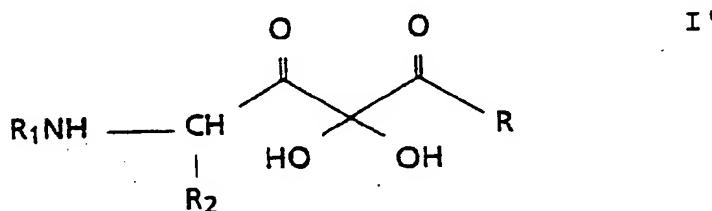
the hydrates, isosteres or the pharmaceutically acceptable salts thereof wherein:

$\text{R}_1$  is an amino protecting group selected from Group K, an  $\alpha$ -amino acid or a peptide comprised of a number of  $\alpha$ -amino acid building blocks, each of said  $\alpha$ -amino acid or peptide optionally bearing an amino protecting group preferably selected from Group K,

$\text{R}_2$  is a side chain of an  $\alpha$ -amino acid building block responsible for directing the inhibitor to the active site of the enzyme, and

$\text{R}$  is  $-\text{OR}^1$  or  $-\text{NR}^2\text{R}^3$  wherein,  $\text{R}^1$ ,  $\text{R}^2$ , and  $\text{R}^3$  are each independently selected from hydrogen, a  $(\text{C}_1-\text{C}_6)$ alkyl group,  $(\text{C}_2-\text{C}_6)$ alkanoyl, phenyl, benzyl, benzoyl, cyclohexyl, cyclohexylmethyl or 2-pyridylmethyl.

Hydrates of the tri keto compounds having structure I are



much more chemically stable than are the unhydrated tri keto compounds of formula I. For this reason, the hydrates are preferred and any reference in this specification and claims to a tri keto (COCOCO) compound should be taken to include reference to the corresponding hydrated form as context allows. Moreover, the compounds of this invention are expected to be in the hydrated form under normal physiological conditions.

Isosteres of the compounds of formula I include those wherein (a) one or more of the  $\alpha$ -amino acid residues of the  $R_1$  substituent is in its unnatural configuration (when there is a natural configuration) or (b) wherein the normal peptidic amide linkage is modified, such as for example, to form  $-\text{CH}_2\text{NH}-$  (reduced),  $-\text{COCH}_2-$  (keto),  $-\text{CH}(\text{OH})\text{CH}_2-$  (hydroxy),  $-\text{CH}(\text{NH}_2)\text{CH}_2-$  (amino),  $-\text{CH}_2\text{CH}_2-$  (hydrocarbon). Preferably a compound of the invention should not be in an isosteric form, particularly it is preferred that there be no modified peptidic amide group in the  $R_1$  group, but if there is, it is preferable to keep the isosteric modifications to a minimum.

Unless otherwise stated, the  $\alpha$ -amino acid building blocks of these peptidase substrate analogs are preferably in their L-configuration. As is conventional nomenclature used by peptide chemists, the code for an amino acid wherein the first (or other) letter of the code is upper case indicates that the amino acid has the natural "L" configuration and wherein the first (or other) letter of the code is lower case indicates that the amino acid has "D" configuration. Throughout this specification reference will be made to lower case amino acid codes or codes preceded by "(D)-" and these shall both be taken as equivalent.

Those compounds of this invention having aspartic or glutamic acid moieties may be in free form or a salt form, e.g., acid addition or anionic salt. Such a compound may be converted into its salt or base form in an art-known manner, one from another. Preferred salts are trifluoroacetate, hydrochloride, sodium, potassium, or ammonium salts, although the scope of salts embraced herein is not limited thereto, the scope being extended to include all of the salts known to be used in the art of peptide chemistry.

Before further defining and/or illustrating the scope of the peptidase inhibitors embraced by formula I, it may be convenient to state some of the more basic concepts related to peptides. Each  $\alpha$ -amino acid has a characteristic "R-group", the R-group being the side chain, or residue, attached to the  $\alpha$ carbon atom of the  $\alpha$ -amino acid. For example, the R-group side chain for glycine is hydrogen, for alanine it is methyl, for valine it is isopropyl. (Thus, throughout this specification the  $R_2$  moiety is the R-group for each indicated  $\alpha$ -amino acid). For the specific R-groups - or side chains - of the  $\alpha$ -amino acids reference to A.L. Lehninger's text on Biochemistry (see particularly Chapter 4) is helpful.

As a further convenience for defining the scope of the compounds embraced by the generic concept of formula I, as well as the sub-generic concepts relating to each of the individual enzymes involved in this invention, various  $\alpha$ -amino acids have been classified into a variety of groups which impart similar functional characteristics for each of the specific enzymes to be inhibited by the peptidase substrates of formula I. These groups are set forth in Table II and the recognized abbreviations for the  $\alpha$ -amino acid blocks are set forth in Table I.

TABLE I

<u>AMINO ACID</u>	<u>SYMBOL</u>
Alanine	Ala
Arginine	Arg
Asparagine	Asn
Aspartic acid	Asp
Asn + Asp	Asx
Cysteine	Cys
Glutamine	Gln
Glutamic acid	Glu
Gln + Glu	Glx
Glycine	Gly
Histidine	His
Isoleucine	Ile
Leucine	Leu
Lysine	Lys
Methionine	Met
Phenylalanine	Phe
p-Guanidinophenylalanine	Phe(Gua)
Proline	Pro
Serine	Ser
Threonine	Thr
Tryptophan	Trp
Tyrosine	Tyr
Valine	Val
Norvaline	Nva
Norleucine	Nle
1-Naphthylalanine	Nal(1)
2-Indolinecarboxylic acid	Ind

TABLE I

<u>AMINO ACID</u>	<u>SYMBOL</u>
Sarcosine	Sar
Cyclohexylalanine	Cha
beta-Alanine	bAla
beta-Valine	bVal
O-4'-Methyltyrosine	Tyr(Me)
3-Pyrazolylalanine	Ala(3pyr)
4-Pyrimidinylalanine	Ala(4pyr)
N <sup>6</sup> -(2-carboxybenzoyl)lysine	Lys(2CBz)
Terephthaloyl	tPht
N <sup>6</sup> -acetyllysine	Lys(Ac)

TABLE II

Group A: Lys and Arg

B: Glu, Asp

C: Ser, Thr, Gln, Asn, Cys, His, Ala(3pyr), Ala(4pyr), and N-methyl derivatives

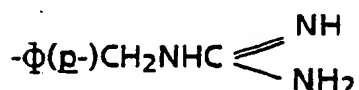
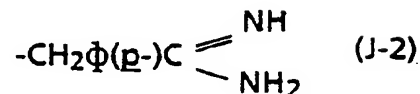
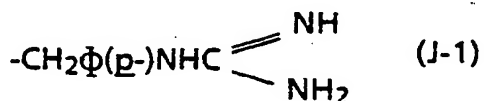
D: Pro, Ind

E: Ala, bAla, Leu, Ile, Val, Nva, bVal, Met, Nle and N-methyl derivatives

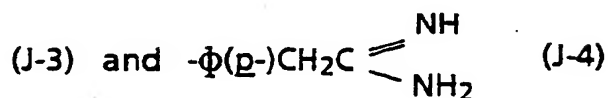
F: Phe, Tyr, Tyr(Me), Ala(3pyr), Ala(4pyr), Trp, Nal(1), and N-methyl derivatives

G: Gly, Sar

J:



(J-3)

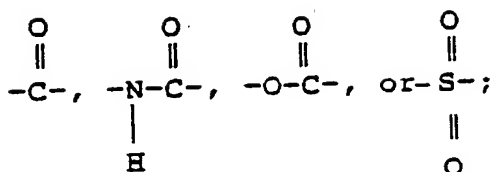


with  $\Phi$  representing phenyl (it being understood that the bond of J-1 to J-4 is always attached to an amino acid)

K: Acetyl (Ac), Succinyl (Suc), Benzoyl (Bz), t-Butyloxycarbonyl (BoC), Carbobenzyloxy (Cbz), Tosyl (Ts), Dansyl (Dns), Isovaleryl (Iva), Methoxysuccinyl (MeOSuc), 1-Adamantanesulfonyl (AdSO<sub>2</sub>), 1-Adamantaneacetyl (AdAc), 2-Carboxybenzoyl (2CBz), Phenylacetyl (PhAc), t-Butylacetyl (Tba), bis[(1-naphthyl)methyl]acetyl (BNMA),

or -A-R<sub>z</sub> wherein

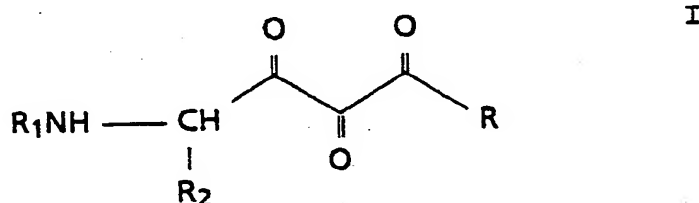
A is



and

$R_z$  is an aryl group containing 6, 10 or 12 carbons suitably substituted by 1 to 3 members selected independently from the group consisting of fluoro, chloro, bromo, iodo, trifluoromethyl, hydroxy, alkyl containing from 1 to 6 carbons, alkoxy containing from 1 to 6 carbons, carboxy, alkylcarbonylamino wherein the alkyl group contains 1 to 6 carbons, 5-tetrazolyl, and acylsulfonamido (i.e., acylaminosulfonyl and sulfonylamino) containing from 1 to 15 carbons, provided that when the acylsulfonamido contains an aryl the aryl may be further substituted by a member selected from fluoro, chloro, bromo, iodo and nitro; and such other terminal amino protecting groups which are functionally equivalent thereto.

In light of the foregoing, the defined compounds of formula I may also be stated as being



the hydrates, isosteres or the pharmaceutically acceptable salts thereof wherein:

R is  $-\text{OR}^1$  or  $-\text{NR}^2\text{R}^3$  wherein,  $\text{R}^1$ ,  $\text{R}^2$ , and  $\text{R}^3$  are each independently selected from hydrogen, a  $(\text{C}_1-\text{C}_6)$  alkyl group,  $(\text{C}_2-\text{C}_6)$  alkanoyl, phenyl, benzyl, benzoyl, cyclohexyl, cyclohexylmethyl or 2-pyridylmethyl,

$\text{R}_1$  is an amino protecting group selected from Group K, an  $\alpha$ -amino acid or a peptide comprised of a number of  $\alpha$ -amino acid building blocks, each of said  $\alpha$ -amino acid or peptide optionally bearing an amino protecting group preferably selected from Group K, and

$\text{R}_2$  is a side chain of an  $\alpha$ -amino acid responsible for directing the inhibitor to the active site of the enzyme wherein the said  $\alpha$ -amino acid and peptide moieties are building blocks selected from Groups A, B, C, D, E, F and G, or wherein  $\text{R}_2$  is a member of the group J, and K is a terminal amino protecting group, members of those groups being

Group A: Lys and Arg

B: Glu, Asp

C: Ser, Thr, Gln, Asn, Cys, His, Ala (3pyr), Ala (4pyr) and N-methyl derivatives

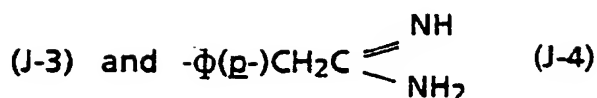
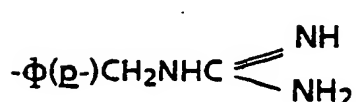
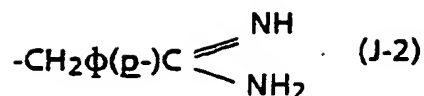
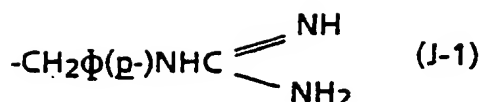
D: Pro, Ind

E: Ala, bAla, Leu, Ile, Val, Nva, bVal, Met, Nle and N-methyl derivatives

F: Phe, Tyr, Trp, Tyr (Me), Ala (3pyr), Ala (4pyr), Nal (1), and N-methyl derivatives

G: Gly, Sar

J:

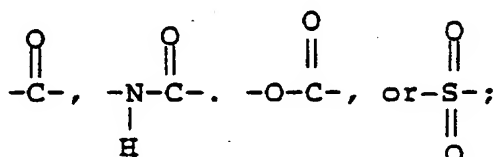


with  $\Phi$  representing phenyl (it being understood that the bond of J-1 to J-4 is always attached to an amino acid)

K. Acetyl (Ac), Succinyl (Suc), Benzoyl (Bz), t-Butyloxycarbonyl (Boc), Carbobenzyloxy (Cbz), Tosyl (Ts), Dansyl (Dns), Isovaleryl (Iva), Methoxysuccinyl (MeOSuc), 1-Adamantanesulfonyl (AdSO<sub>2</sub>), 1-Adamantaneacetyl (AdAc), 2-Carboxy benzoyl (2CBz), Phenylacetyl (PhAc), t-Butylacetyl (Tba), bis[(1-naphthyl)methyl]acetyl (BNMA),

or -A-R<sub>2</sub> wherein

A is



and

R<sub>2</sub> is an aryl group containing 6, 10 or 12 carbons suitably substituted by 1 to 3 members selected independently from the group consisting of fluoro, chloro, bromo, iodo, trifluoromethyl, hydroxy, alkyl containing from 1 to 6 carbons, alkoxy containing from 1 to 6 carbons, carboxy, alkylcarbonylamino wherein the alkyl group contains 1 to 6 carbons, 5-tetrazolyl, and acylsulfonamido (i.e., acylaminosulfonyl and sulfonylaminocarbonyl "Sac") containing from 1 to 15 carbons, provided that when the acylsulfonamido contains an aryl the aryl may be further substituted by a member selected from fluoro, chloro, bromo, iodo and nitro; and such other terminal amino protecting groups which are functionally equivalent thereto.

The compounds of formula I can also be depicted as a peptide derivative, albeit modified on its carboxy terminal end. In this depiction the R<sub>2</sub> moiety is in the P<sub>1</sub> position of the peptide, the  $\alpha$ -amino acids of the R<sub>1</sub> moiety would be in the P<sub>2</sub>→P<sub>n</sub> positions, n being the numeric sequence dependent upon the number of  $\alpha$ -amino acids in that particular compound, e.g., if R<sub>1</sub> contained four  $\alpha$ -amino acids it would be comprised of P<sub>2</sub>-P<sub>3</sub>-P<sub>4</sub>-P<sub>5</sub> positions with the option of a terminal amino protecting group from Group K in the P<sub>5</sub> moiety.

To further illustrate the shorthand nomenclature used throughout this application assume that R<sub>1</sub> is comprised of P<sub>2</sub>, P<sub>3</sub>, P<sub>4</sub> having a terminal amino protecting group so that R<sub>1</sub> is -Pro-Ala-Ala-MeOSuc, R<sub>2</sub> is isopropyl, then that specific compound would be written as MeOSuc-Ala-Ala-Pro-Val.

It is also to be noted that in some instances it is more convenient to designate the terminal amino protecting group as a separate P<sub>n</sub> position of the peptide. The terminal amino protecting group would be designated as being in the P<sub>5</sub> position and thus R<sub>1</sub> would be P<sub>2</sub>-P<sub>3</sub>-P<sub>4</sub>-P<sub>5</sub> with P<sub>5</sub> being a protecting group of Group K. If P<sub>4</sub> optionally is deleted, then quite obviously, when P<sub>4</sub> is deleted the protecting group of P<sub>5</sub> would be attached to the P<sub>3</sub> moiety. In those instances wherein Group K represents an -A-R<sub>2</sub> moiety, it is preferred that A represent -C(=O)- and that R<sub>2</sub> represent acylsulfonamido, particularly those wherein the acylsulfonamido contains an aryl moiety (preferably phenyl) substituted by a halogen, the preferred -A-R<sub>2</sub> moieties being 4-[(4-chlorophenyl)sulfonylaminocarbonyl]phenylcarbonyl, 4-[(4-bromophenyl)sulfonylaminocarbonyl]phenylcarbonyl and 4-[phenylsulfonylaminocarbonyl]phenylcarbonyl (said moieties being abbreviated as Cl $\Phi$ SacBZ, Br $\Phi$ SacBz and  $\Phi$ SacBz, respectively).

Utilizing the foregoing illustrations those compounds of formula I which are useful as inhibitors for human leukocyte elastase are represented by the formula Ia:

$R_1NHCH(R_2)C(=O)C(=O)C(=O)R$  (Ia)

and the hydrates, isosteres or the pharmaceutically acceptable salts thereof, wherein

R is  $-OR^1$  or  $-NR^2R^3$  wherein,  $R^1$ ,  $R^2$ , and  $R^3$  are each independently selected from hydrogen, a ( $C_1$ - $C_6$ -)alkyl group, ( $C_2$ - $C_6$ )alkanoyl, phenyl, benzyl, benzoyl, cyclohexyl, cyclohexylmethyl or 2-pyridylmethyl with

NH<sub>2</sub> being preferred,

$R_1$  is  $P_2$ - $P_3$ - $P_4$ - $P_5$  with

$P_2$  being an  $\alpha$ -amino acid selected from Groups D, E and F, with proline being preferred,

$P_3$  is an  $\alpha$ -amino acid of Groups D and E, or is lysine with isoleucine, valine or alanine being preferred,

$P_4$  is an  $\alpha$ -amino acid of Group E or is deleted with alanine being preferred, and

$P_5$  is a terminal moiety of Group K with methoxysuccinyl and Cbz and  $Cl\Phi$ SacBz,  $Br\Phi$ SacBz and  $\Phi$ SacBz being preferred, and

$R_2$  is the side chain of an  $\alpha$ -amino acid of Groups E and G, with the side chain of norvaline and valine being preferred.

Human leukocyte elastase is released by polymorphonuclear leukocytes at sites of inflammation and thus is a contributing cause for a number of disease states. Thus the peptidase substrates of formula (Ia) have an anti-inflammatory effect useful in the treatment of gout, rheumatoid arthritis and other inflammatory diseases, and in the treatment of emphysema. In their end-use application the enzyme inhibitory properties of the compounds of (Ia) are readily ascertained by standard biochemical techniques well known in the art. Potential dose range for their end-use application will of course depend upon the nature and severity of the disease state as determined by the attending diagnostician with the range of 0.01 to 10 mg/kg body weight per day being useful for the aforementioned disease states with 0.1 mg to 10 mg/kg per day being preferred. The preferred compounds for this enzyme are:

MeOSuc-Ala-Ala-Pro-Val-C(O)C(O)NH<sub>2</sub>,

AdSO<sub>2</sub>-Lys(2CBz)-Pro-Val-C(O)C(O)NH<sub>2</sub>,

CBz-Val-Pro-Val-C(O)C(O)NH<sub>2</sub>,

$Cl\Phi$ SacBz-Val-Pro-Val-C(O)C(O)NH<sub>2</sub>,

$Br\Phi$ SacBz-Val-Pro-Val-C(O)C(O)NH<sub>2</sub>,

$\Phi$ SacBz-Val-Pro-Val-C(O)C(O)NH<sub>2</sub>, and

tPht-Val-Pro-Val-C(O)C(O)NH<sub>2</sub>.

Those compounds of formula I which are useful as inhibitors of Cathepsin G are represented by the structural formula Ib:

$R_1NHCH(R_2)C(=O)C(=O)C(=O)R$  (Ib)

and the hydrates, isosteres or the pharmaceutically acceptable salts thereof, wherein

R is  $-OR^1$  or  $-NR^2R^3$  wherein,  $R^1$ ,  $R^2$ , and  $R^3$  are each independently selected from hydrogen, a ( $C_1$ - $C_6$ )alkyl group, ( $C_2$ - $C_6$ )alkanoyl, phenyl, benzyl, benzoyl, cyclohexyl, cyclohexylmethyl or 2-pyridylmethyl with OH being preferred,

R<sub>1</sub> is  $-P_2$ - $P_3$ - $P_4$ - $P_5$  with

$P_2$  being selected from Groups D, E, and G, with proline being preferred;

$P_3$  is selected from Groups E and G with alanine and valine being preferred,

$P_4$  is selected from Groups E and G or is deleted with alanine being preferred, the terminal  $\alpha$ -amino acid optionally bearing a protecting group selected from Group K with succinyl,  $Cl\Phi$ SacBz or other Sac containing groups or methoxysuccinyl being preferred, and

$R^2$  is selected from side chains of the amino acids of Groups E and F and preferably is benzyl.

The end-use application of the compounds (Ib) inhibiting Cathepsin G is the same as for human leukocyte inhibitors, including arthritis, gout and emphysema, but also embracing the treatment of glomerulonephritis and lung infestations caused by infections in the lungs. For their end-use application, the potency and other biochemical parameters of the enzyme inhibiting characteristics of the compounds of (Ib) are readily ascertained by standard biochemical techniques well known in the art. Actual dose ranges for their specific end-use application will, of course, depend upon the nature and severity of the disease state of the patient or animal to be treated as determined by the attending diagnostician. It is to be expected that the general end-use application dose range will be about 0.01 to 10 mg/kg per day for an effective therapeutic effect with 0.1 to 10 mg/kg per day being preferred. Preferred compounds for formula (Ib) are:

MeOSuc-Ala-Ala-Pro-Phe-C(O)C(O)OH,

Suc-Ala-Ala-Pro-Phe-C(O)C(O)OH, and

$Cl\Phi$ SacBz-Val-Pro-Phe-C(O)C(O)OH.

Those compounds of formula I which are useful as inhibitors of thrombin are represented by the formula Ic:

$R_1NHCH(R_2)C(=O)C(=O)C(=O)R$  (Ic)



and the hydrates, isosteres or the pharmaceutically acceptable salts thereof, wherein

R is  $-OR^1$  or  $-NR^2R^3$  wherein,  $R^1$ ,  $R^2$ , and  $R^3$  are each independently selected from hydrogen, a  $(C_1-C_6)$ alkyl group,  $(C_2-C_6)$ alkanoyl, phenyl, benzyl, benzoyl, cyclohexyl, cyclohexylmethyl or 2-pyridylmethyl with  $OR^1$  being preferred,

5  $R_1$  is (a)  $-P_2-P_3$ , (b)  $-P_2$  or (c)  $-P_2-P_3-P_4$  wherein:

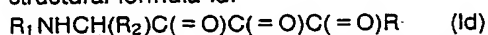
(a)  $P_2$  is selected from Groups D, E and F, preferably proline,  $P_3$  is selected from Group F, each  $P_3$  is selected from Group F being in the D-configuration, preferably Phe,

(b)  $P_2$  is selected from Group K and preferably is dansyl, tosyl or benzoyl, or

10 (c)  $P_2$  is selected from Group E and preferably is alanine,  $P_3$  is selected from Groups C, G and E and preferably is serine,  $P_4$  is selected from Groups F, G and E or is deleted and preferably is Phe, and  $R_2$  is preferably the arginine side chain but may also be selected from side chains of the amino acids of Group A or is a member of Group J, preferably (J-1).

The compounds embraced by formula (Ic) inhibit thrombin and therefore, as in the use of heparin, the compounds may be used as the initial anticoagulant agent in thrombophlebitis and coronary thrombosis. For 15 their end-use application, the potency and other biochemical parameters of the enzyme inhibiting characteristics of the compounds of (Ic) are readily ascertained by standard biochemical techniques well known in the art. Actual dose ranges for their specific end-use application will, of course, depend upon the nature and severity of the disease state of the patient or animal to be treated as determined by the attending diagnostician. It is to be expected that the general end-use application dose range will be about 0.01 to 10 20 mg/kg per day for an effective therapeutic effect with 0.1 mg to 10 mg/kg per day being preferred. Preferred compounds are as expressed for Cathepsin G and also include: phe-Pro-NRCH(J-1)-C(O)C(O)OH, phe-Pro-Arg-C(O)C(O)OH, Dns-Arg-C(O)C(O)OH, Phe-Ser-Ala-C(O)C(O)OH, 25 phe-Pro-Lys-C(O)C(O)OH, and Bz-NHCH(J-1)-C(O)C(O)OH.

The compounds of formula I which are useful as inhibitors of chymotrypsin are represented by the structural formula Id:



30 and the hydrates, isosteres or the pharmaceutically acceptable salts thereof, wherein R is  $-OR^1$  or  $-NR^2R^3$  wherein,  $R^1$ ,  $R^2$ , and  $R^3$  are each independently selected from hydrogen, a  $(C_1-C_6)$ alkyl group,  $(C_2-C_6)$ alkanoyl, phenyl, benzyl, benzoyl, cyclohexyl, cyclohexylmethyl or 2-pyridylmethyl with  $OR^1$  being preferred especially wherein  $R^1$  is a methyl group,

$R_1$  is  $-P_2-P_3-P_4-P_5$  with

35  $P_2$  being selected from Groups D and E, with Leu being preferred, or from Groups G and K with benzoyl being preferred,

$P_3$  is selected from Groups E, G, and K, or is deleted, with alanine and acetyl being preferred,

$P_4$  is selected from Groups E, G, and K or is deleted, with alanine being preferred, and

$P_5$  is selected from Group K with succinyl being preferred or is deleted, and

40  $R_2$  is selected from the side chains of the amino acids of Groups E and F but preferably is the Phe side chain or the Tyr side chain.

The end-use application of the compounds (Id) inhibiting chymotrypsin is in the treatment of pancreatitis. For their end-use application, the potency and other biochemical parameters of the enzyme inhibiting characteristics of the compounds of (Id) are readily ascertained by standard biochemical 45 techniques well known in the art. Actual dose ranges for their specific end-use application will, of course, depend upon the nature and severity of the disease state of the patient or animal to be treated as determined by the attending diagnostician. It is to be expected that the general end-use application dose range will be about 0.01 to 10 mg/kg per day for an effective therapeutic effect with 0.1 mg to 10 mg/kg per day being preferred. Preferred compounds are as expressed for Cathepsin G and also include:

50 Bz-Phe-C(O)C(O)OCH<sub>3</sub>,

Bz-Tyr-C(O)C(O)OCH<sub>3</sub>, and

Ac-Leu-Phe-C(O)C(O)OCH<sub>3</sub>.

The compounds of formula I which are useful as inhibitors of trypsin are represented by the structural formula Ie:



and the hydrates, isosteres or the pharmaceutically acceptable salts thereof, wherein

R is  $-OR^1$  or  $-NR^2R^3$  wherein,  $R^1$ ,  $R^2$ , and  $R^3$  are each independently selected from hydrogen, a  $(C_1-C_6)$ alkyl group,  $(C_2-C_6)$ alkanoyl, phenyl, benzyl, benzoyl, cyclohexyl, cyclohexylmethyl or 2-pyridylmethyl with  $OR^1$

being preferred,

R<sub>1</sub> is selected from (a) -P<sub>2</sub>-P<sub>3</sub>, (b) -P<sub>2</sub> or (c) -P<sub>2</sub>-P<sub>3</sub>-P<sub>4</sub> with

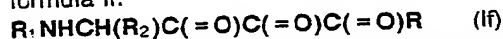
(a) P<sub>2</sub> is selected from Groups D, E and F and is preferably proline or alanine, P<sub>3</sub> is selected from Group F, (each being in the D configuration) and preferably is Phe,

(b) P<sub>2</sub> is selected from Group K and preferably is dansyl, tosyl or benzoyl, and

(c) P<sub>2</sub> is selected from Group D and E and preferably is proline or alanine, P<sub>3</sub> is selected from Groups G and E or preferably is serine, P<sub>4</sub> is selected from Groups G and E or is deleted or preferably is Phe, and R<sub>2</sub> is preferably the arginine side chain but may also be selected from side chains of the amino acids of Groups A or is a member of Group J, preferably (J-1).

The end-use application of the compounds (Ie) inhibiting trypsin is in the treatment of pancreatitis. For their end-use application, the potency and other biochemical parameters of the enzyme inhibiting characteristics of the compounds of (Ie) are readily ascertained by standard biochemical techniques well known in the art. Actual dose ranges for their specific end-use application will, of course, depend upon the nature and severity of the disease state of the patient or animal to be treated as determined by the attending diagnostician. It is to be expected that the general end-use application dose range will be about 0.01 to 10 mg/kg per day for an effective therapeutic effect with 0.1 mg to 10 mg/kg per day being preferred. The preferred compounds useful for inhibiting trypsin are the same as for the inhibitors of thrombin.

The compounds of formula I which are useful as inhibitors of plasmin are represented by the structural formula If:



and the hydrates, isosteres or the pharmaceutically acceptable salts thereof, wherein

R is -OR<sup>1</sup> or -NR<sup>2</sup>R<sup>3</sup> wherein, R<sup>1</sup>, R<sup>2</sup>, and R<sup>3</sup> are each independently selected from hydrogen, a (C<sub>1</sub>-C<sub>6</sub>)alkyl group, (C<sub>2</sub>-C<sub>6</sub>)alkanoyl, phenyl, benzyl, benzoyl, cyclohexyl, cyclohexylmethyl or 2-pyridylmethyl with OR<sup>1</sup> being preferred especially wherein R<sup>1</sup> is a hydrogen or a methyl group,

R<sub>1</sub> is -P<sub>2</sub>-P<sub>3</sub>-P<sub>4</sub> with

P<sub>2</sub> being selected from Group E and F and preferably is Ala or Phe,

P<sub>3</sub> is selected from Groups B, F and K and preferably is Glu or acetyl, and

P<sub>4</sub> is selected from Group K or is deleted and preferably is dansyl, and

R<sub>2</sub> is selected from a side chain of an amino acid of Group A or is a member of Group J but preferably is the side chain of lysine or is (J-1).

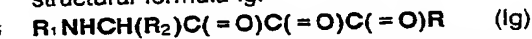
The compounds embraced by formula (If) inhibit plasmin and are therefore antiproliferative agents useful in treating excessive cell growth, particularly in the treatment of benign prostatic hypertrophy and prostatic carcinoma, and in the treatment of psoriasis. For their end-use application, the potency and other biochemical parameters of the enzyme inhibiting characteristics of the compounds of (If) are readily ascertained by standard biochemical techniques well known in the art. Actual dose ranges for their specific end-use application will, of course, depend upon the nature and severity of the disease state of the patient or animal to be treated as determined by the attending diagnostician. It is to be expected that the general end-use application dose range will be about 0.01 to 10 mg/kg per day for an effective therapeutic effect with 0.1 to 10 mg/kg per day being preferred. The preferred compounds are:

Dns-Glu-Phe-Lys-C(O)C(O)OCH<sub>3</sub>,

Ac-Ala-NHCH(J-1)-C(O)C(O)OCH<sub>3</sub>, and

Ac-Ala-Lys-C(O)C(O)OCH<sub>3</sub>.

The compounds of formula I which are useful as inhibitors of C<sub>1</sub>-esterase are represented by the structural formula Ig:



and the hydrates, isosteres or the pharmaceutically acceptable salts thereof wherein

R is -OR<sup>1</sup> or -NR<sup>2</sup>R<sup>3</sup> wherein, R<sup>1</sup>, R<sup>2</sup>, and R<sup>3</sup> are each independently selected from hydrogen, a (C<sub>1</sub>-C<sub>6</sub>)alkyl group, (C<sub>2</sub>-C<sub>6</sub>)alkanoyl, phenyl, benzyl, benzoyl, cyclohexyl, cyclohexylmethyl or 2-pyridylmethyl with NH<sub>2</sub> or OR<sup>1</sup> being preferred especially wherein R<sup>1</sup> is a hydrogen or a methyl group,

R<sub>1</sub> generically is -P<sub>2</sub>-P<sub>3</sub> with P<sub>2</sub> being selected from Groups E, G, D, C, F, A and B with Ala being preferred, and P<sub>3</sub> is selected from Group K with Cbz or acetyl being preferred, and

R<sub>2</sub> is selected from the side chain of an amino acid of Group A or is a member of Group J, but preferably the side chain of Arg or is (J-1).

The compounds embraced by formula (Ig) inhibit C<sub>1</sub>-esterase and are therefore useful in treating systemic lupus, arthritis, autoimmune hemolytic anemia and glomerulonephritis. For their end-use application, the potency and other biochemical parameters of the enzyme inhibiting characteristics of the compounds of (Ig) is readily ascertained by standard biochemical techniques well known in the art. Actual dose ranges for their specific end-use application will, of course, depend upon the nature and severity of

the disease state of the patient or animal to be treated as determined by the attending diagnostician. It is to be expected that the general end-use application dose range will be about 0.01 to 10 mg/kg per day for an effective therapeutic effect with 0.1 mg to 10 mg/kg per day being preferred. The preferred compounds are: Cbz-Ala-Arg-C(O)C(O)NH<sub>2</sub> and

- 5 Ac-Ala-NHCH(J-1)-C(O)C(O)OCH<sub>3</sub>.

The compounds of formula I which are useful as inhibitors of C<sub>3</sub>-convertase are represented by the formula I<sub>h</sub>:



and the hydrates, isosteres or the pharmaceutically acceptable salts thereof, wherein

- 10 R is -OR<sup>1</sup> or -NR<sup>2</sup>R<sup>3</sup> wherein, R<sup>1</sup>, R<sup>2</sup>, and R<sup>3</sup> are each independently selected from hydrogen, a (C<sub>1</sub>-C<sub>6</sub>)alkyl group, (C<sub>2</sub>-C<sub>6</sub>)alkanoyl, phenyl, benzyl, benzoyl, cyclohexyl, cyclohexylmethyl or 2-pyridylmethyl with NH<sub>2</sub> or OR<sup>1</sup> being preferred especially wherein R<sup>1</sup> is a hydrogen or a methyl group,

R<sub>1</sub> is -P<sub>2</sub>-P<sub>3</sub>-P<sub>4</sub> with

P<sub>2</sub> being selected from Groups E and F, with Ala being preferred,

- 15 P<sub>3</sub> is selected from Groups E and F with Leu being preferred, and

P<sub>4</sub> is selected from Group K with Bz being preferred, and

R<sub>2</sub> is selected from the side chain of an amino acid of Group A or is a member of Group J, with Arg being preferred.

- 20 The compounds embraced by formula (Ih) inhibit C<sub>3</sub>-convertase and are therefore useful in treating systemic lupus, arthritis, autoimmune hemolytic anemia and glomerulonephritis. For their end-use application, the potency and other biochemical parameters of the enzyme inhibiting characteristics of the compounds of (Ih) are readily ascertained by standard biochemical techniques well known in the art. Actual dose ranges for their specific end-use application will, of course, depend upon the nature and severity of the disease state of the patient or animal to be treated as determined by the attending diagnostician. It is to be expected that the general end-use application dose range will be about 0.01 to 10 mg/kg per day for an effective therapeutic effect with 0.1 mg to 10 mg/kg per day being preferred. The preferred compound is: Bz-Leu-Ala-Arg-C(O)C(O)NH<sub>2</sub>.

The compounds of formula I which are useful as inhibitors of Urokinase are represented by the formula I<sub>i</sub>:

- 30  $\text{R}_1\text{NHCH(R}_2\text{)C(=O)C(=O)C(=O)R} \quad (\text{Ii})$

and the hydrates, isosteres or the pharmaceutically acceptable salts thereof, wherein

R is -OR<sup>1</sup> or -NR<sup>2</sup>R<sup>3</sup> wherein, R<sup>1</sup>, R<sup>2</sup>, and R<sup>3</sup> are each independently selected from hydrogen, a (C<sub>1</sub>-C<sub>6</sub>)alkyl group, (C<sub>2</sub>-C<sub>6</sub>)alkanoyl, phenyl, benzyl, benzoyl, cyclohexyl, cyclohexylmethyl or 2-pyridylmethyl with or NH<sub>2</sub> or OR<sup>1</sup> being preferred especially wherein R<sup>1</sup> is a hydrogen or a methyl group,

- 35 R<sub>1</sub> is -P<sub>2</sub>-P<sub>3</sub> with

P<sub>2</sub> being selected from Groups E and G with Ala and Gly being preferred and

P<sub>3</sub> is selected from Group B with Glu being preferred, and

R<sub>2</sub> is selected from the side chain of an amino acid of Group A or is a member of Group J with the side chain of Arg being preferred.

- 40 The compounds embraced by formula (Ii) inhibit Urokinase and therefore are useful in treating excessive cell growth disease states. As such compounds are useful in the treatment of benign prostatic hypertrophy and prostatic carcinoma, the treatment of psoriasis, and in their use as abortifacients. For their end-use application, the potency and other biochemical parameters of the enzyme inhibiting characteristics of the compounds of (Ii) are readily ascertained by standard biochemical techniques well known in the art. Actual dose ranges for their specific end-use application will, of course, depend upon the nature and severity of the disease state of the patient or animal to be treated as determined by the attending diagnostician. It is to be expected that the general end-use application dose range will be about 0.01 to 10 mg/kg per day for an effective therapeutic effect with 0.1 mg to 10 mg/kg per day being preferred. The preferred compounds are:

- 50 K-Glu-Gly-Arg-C(O)C(O)NH<sub>2</sub> and

K-Glu-Gly-Phe(Gua)-C(O)C(O)NH<sub>2</sub>,

The compounds of formula I which are useful as inhibitors of plasminogen activator are represented by the structural formula I<sub>j</sub>:



- 55 and the hydrates, isosteres or the pharmaceutically acceptable salts thereof, wherein

R is -OR<sup>1</sup> or -NR<sup>2</sup>R<sup>3</sup> wherein, R<sup>1</sup>, R<sup>2</sup>, and R<sup>3</sup> are each independently selected from hydrogen, a (C<sub>1</sub>-C<sub>6</sub>)alkyl group, (C<sub>2</sub>-C<sub>6</sub>)alkanoyl, phenyl, benzyl, benzoyl, cyclohexyl, cyclohexylmethyl or 2-pyridylmethyl with NH<sub>2</sub> or OR<sup>1</sup> being preferred especially wherein R<sup>1</sup> is a hydrogen or a methyl group,

R<sub>1</sub> is -P<sub>2</sub>-P<sub>3</sub>-P<sub>4</sub> wherein

P<sub>2</sub> is Gly,

P<sub>3</sub> is selected from Group B with Glu being preferred, and

P<sub>4</sub> is selected from Group K and preferably is dansyl, and

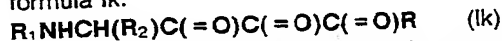
- 5 R<sub>2</sub> is selected from a side chain of an amino acid of Group A or is a member of Group J with the side chain of Arg being preferred.

Preferred compounds are:

Dns-Glu-Gly-Arg-C(O)C(O)NH<sub>2</sub> and

Dns-Glu-Gly-Phe(Gua)-C(O)C(O)NH<sub>2</sub>.

- 10 The compounds of formula I which are useful as inhibitors of acrosin are represented by the structural formula Ik:



and the hydrates, isosteres or the pharmaceutically acceptable salts thereof, wherein

- 15 R is -OR<sup>1</sup> or -NR<sup>2</sup>R<sup>3</sup> wherein, R<sup>1</sup>, R<sup>2</sup>, and R<sup>3</sup> are each independently selected from hydrogen, a (C<sub>1</sub>-C<sub>6</sub>)alkyl group, (C<sub>2</sub>-C<sub>6</sub>)alkanoyl, phenyl, benzyl, benzoyl, cyclohexyl, cyclohexylmethyl or 2-pyridylmethyl with NH<sub>2</sub> or OR<sup>1</sup> being preferred especially wherein R<sup>1</sup> is a hydrogen or a methyl group,

R<sub>1</sub> is -P<sub>2</sub>-P<sub>3</sub>-P<sub>4</sub> with

P<sub>2</sub> being selected from Groups E or K with Leu or benzoyl being preferred,

P<sub>3</sub> is selected from Group E with Leu being preferred or is deleted, and

- 20 P<sub>4</sub> is selected from Group K with Boc being preferred or is deleted, and

R<sub>2</sub> is selected from the side chains of the amino acids of Group A or the members of Group J with the side chains of Arg and (J-1) being preferred.

The preferred compounds are:

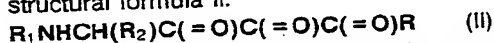
Boc-Leu-Leu-Arg-C(O)C(O)NH<sub>2</sub>,

- 25 Boc-Leu-Leu-Phe(Gua)-C(O)C(O)OCH<sub>3</sub>, and

Bz-NHCH(J-1)-C(O)C(O)NH<sub>2</sub>.

- The compounds of formula (Ik) are acrosin inhibitors and therefore are useful as anti-fertility agents in that they possess the characteristics of preventing sperm from penetrating an otherwise fertilizable egg. For their end-use application, the potency and other biochemical parameters of the enzyme inhibiting characteristics of the compounds of (Ik) are readily ascertained by standard biochemical techniques well known in the art. Actual dose ranges for their specific end-use application will, of course, depend upon the state of the patient or animal to be treated as determined by the attending diagnostician. It is to be expected that the general end-use application dose range will be about 0.01 to 10 mg/kg per day for an effective therapeutic effect with 0.1 mg to 10 mg/kg per day being preferred.

- 35 The compounds of formula I which are useful as inhibitors of  $\beta$ -lactamase are represented by the structural formula II:



and the hydrates, isosteres or the pharmaceutically acceptable salts thereof wherein

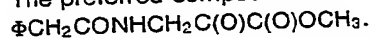
- 40 R is -OR<sup>1</sup> or -NR<sup>2</sup>R<sup>3</sup> wherein, R<sup>1</sup>, R<sup>2</sup>, and R<sup>3</sup> are each independently selected from hydrogen, a (C<sub>1</sub>-C<sub>6</sub>)alkyl group, (C<sub>2</sub>-C<sub>6</sub>)alkanoyl, phenyl, benzyl, benzoyl, cyclohexyl, cyclohexylmethyl or 2-pyridylmethyl with NH<sub>2</sub> or OR<sup>1</sup> being preferred especially wherein R<sup>1</sup> is a hydrogen or a methyl group,

R<sub>1</sub> is P<sub>2</sub>,

P<sub>2</sub> being selected from Group K with COCH<sub>2</sub>Φ and Bz being preferred, and

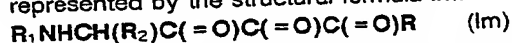
R<sub>2</sub> is selected from a side chain of an amino acid of Groups E, G and C with hydrogen being preferred.

- 45 The preferred compound is:



- The compounds embraced by formula (II) inhibit  $\beta$ -lactamase and therefore are useful in the potentiation of antibacterial agents, particularly the  $\beta$ -lactam antibacterials. For their end-use application, the potency and other biochemical parameters of the enzyme inhibiting characteristics of the compounds of (II) are readily ascertained by standard biochemical techniques well known in the art. Actual dose ranges for their specific end-use application will, of course, depend upon the nature and severity of the disease state of the patient or animal to be treated as determined by the attending diagnostician. It is to be expected that the general end-use application dose range will be about 0.01 to 10 mg/kg per day for an effective therapeutic effect with 0.1 mg to 10 mg/kg per day being preferred.

- 55 The compounds of formula I which are useful as inhibitors of D-Ala-D-Ala carboxypeptidase are represented by the structural formula Im:



and the hydrates, isosteres or the pharmaceutically acceptable salts thereof, wherein

R is -OR<sup>1</sup> or -NR<sup>2</sup>R<sup>3</sup> wherein, R<sup>1</sup>, R<sup>2</sup>, and R<sup>3</sup> are each independently selected from hydrogen, a (C<sub>1</sub>-C<sub>6</sub>)alkyl group, (C<sub>2</sub>-C<sub>6</sub>)alkanoyl, phenyl, benzyl, benzoyl, cyclohexyl, cyclohexylmethyl or 2-pyridylmethyl with NH<sub>2</sub> or OR<sup>1</sup> being preferred especially wherein R<sup>1</sup> is a hydrogen or a methyl group,

R<sub>1</sub> is P<sub>2</sub>-P<sub>3</sub> with

- 5 P<sub>2</sub> being Lys(Ac) or is selected from Groups E and C with Lys(Ac) being preferred, and  
P<sub>3</sub> is selected from Group K with Ac being preferred, and  
R<sub>2</sub> is methyl such that P<sub>1</sub> is D-Ala.

The preferred compound is:

Ac-Lys (Ac)-Ala-C(O)C(O)OH.

- 10 The compounds of formula I which are useful as inhibitors of Cathepsin B are represented by the structural formula In:

**R<sub>1</sub>NHCH(R<sub>2</sub>)C(=O)C(=O)C(=O)R** (In)

and the hydrates, isosteres or the pharmaceutically acceptable salts thereof, wherein

- R is -OR<sup>1</sup> or -NR<sup>2</sup>R<sup>3</sup> wherein, R<sup>1</sup>, R<sup>2</sup>, and R<sup>3</sup> are each independently selected from hydrogen, a (C<sub>1</sub>-C<sub>6</sub>)alkyl group, (C<sub>2</sub>-C<sub>6</sub>)alkanoyl, phenyl, benzyl, benzoyl, cyclohexyl, cyclohexylmethyl or 2-pyridylmethyl with NH<sub>2</sub> or OR<sup>1</sup> being preferred especially wherein R<sup>1</sup> is a hydrogen or a methyl group,  
15 R<sub>1</sub> is (a) -P<sub>2</sub>-P<sub>3</sub> or (b) -P<sub>2</sub>-P<sub>3</sub>-P<sub>4</sub> wherein

- (a) P<sub>2</sub> is selected from Groups E and F with Phe being preferred  
20 and, P<sub>3</sub> is selected from Group K with Cbz being preferred,  
(b) P<sub>2</sub> is selected from Groups E and F with Leu being preferred,

P<sub>3</sub> being selected from Groups E and F with Leu being preferred,

P<sub>4</sub> is selected from Group K with Ac being preferred, and

- 25 R<sub>2</sub> is selected from the side chains of the α-amino acids of Group A or is a member of Group J or is ThrOCH<sub>2</sub>Φ, with the side chain of Arg being preferred.

The preferred compounds are:

Cbz-Phe-NHCH(J-1)-C(O)C(O)OCH<sub>3</sub>,

Ac-Leu-Leu-NHCH(J-1)-C(O)C(O)OH, and

- 30 Ac-Leu-Leu-Arg-C(O)C(O)OH.

The compounds of formula I which are useful as inhibitors of renin are represented by the structural formula Io:

**R<sub>1</sub>NHCH(R<sub>2</sub>)C(=O)C(=O)C(=O)R** (Io)

and the hydrates, isosteres or the pharmaceutically acceptable salts thereof wherein

- 35 R is -OR<sup>1</sup> or -NR<sup>2</sup>R<sup>3</sup> wherein, R<sup>1</sup>, R<sup>2</sup>, and R<sup>3</sup> are each independently selected from hydrogen, a (C<sub>1</sub>-C<sub>6</sub>)alkyl group, (C<sub>2</sub>-C<sub>6</sub>)alkanoyl, phenyl, benzyl, benzoyl, cyclohexyl, cyclohexylmethyl or 2-pyridylmethyl with NH<sub>2</sub> or OH, benzyl, isovaleryl amino (Iva), and 2-pyridylmethyl being preferred,  
R<sub>1</sub> is -P<sub>2</sub>-P<sub>3</sub>-P<sub>4</sub>-P<sub>5</sub>-P<sub>6</sub> wherein

P<sub>2</sub> is selected from Groups E, C and F with His, nVal, Ala(3pyr), Ala(4pyr), and Nle being preferred,

- 40 P<sub>3</sub> is selected from Groups E or F or is deleted with Phe and Tyr(Me) being preferred,

P<sub>4</sub> is selected from Groups E, D, F or is deleted with Pro, bAla or bVal being preferred,

P<sub>5</sub> is selected from Groups E, C, F or is deleted with His being preferred, and

P<sub>6</sub> is selected from Group K with Boc, Cbz and Tba being preferred, or being BNMA when P<sub>3</sub>, P<sub>4</sub>, P<sub>5</sub> are deleted, or when P<sub>4</sub> is bVal or bAla, P<sub>5</sub> and P<sub>6</sub> are deleted, and

- 45 R<sub>2</sub> is selected from a side chain of an amino acid of Groups E or F or is cyclohexylmethylene with the side chain of Leu or cyclohexylmethylene being preferred.

The preferred compounds are:

Cbz-Nal(1)-His-Leu-C(O)C(O)OCH<sub>2</sub>Φ,

Cbz-Phe-His-Leu-C(O)C(O)NHCH<sub>2</sub>Φ,

- 50 Boc-Phe-Nva-Leu-C(O)C(O)NHCH<sub>2</sub>Φ,

Cbz-Phe-Nva-Leu-C(O)C(O)NHCH<sub>2</sub>Φ,

Boc-His-Pro-Phe-His-Leu-C(O)C(O)NHCH<sub>2</sub>(2-pyridyl),

Cbz-Phe-His-Cha-C(O)C(O)OCH<sub>2</sub>Φ,

Cbz-His-Leu-C(O)C(O)NHCH<sub>2</sub>Φ,

- 55 Boc-Phe-His-Leu-C(O)C(O)OCH<sub>2</sub>Φ,

Boc-Phe-Nva-Cha-C(O)C(O)NHCH<sub>2</sub>Φ,

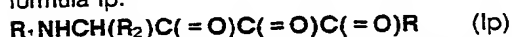
Boc-Tyr(Me)-Nva-Cha-C(O)C(O)Iva,

Boc-Phe-Ala(3pyr)-Cha-C(O)C(O)Iva,

Tba-Tyr(Me)-Nva-Cha-C(O)C(O)Iva,  
 Tba-Tyr(Me)-Ala(4pyr)-Cha-C(O)C(O)Iva,  
 bAla-Tyr(Me)-Nva-Cha-C(O)C(O)Iva,  
 bVal-Tyr(Me)-Nva-Cha-C(O)C(O)Iva,  
 5 bVal-Tyr(Me)-His-Cha-C(O)C(O)Iva, and  
 bAla-Tyr(Me)-His-Cha-C(O)C(O)Iva.

The compounds of formula (lo) inhibit renin and therefore are used as antihypertensive agents useful in treating hypertension. For their end-use application, the potency and other biochemical parameters of the enzyme inhibiting characteristics of the compounds of (lo) are readily ascertained by standard biochemical techniques well known in the art. Actual dose ranges for their specific end-use application will, of course, depend upon the nature and severity of the disease state of the patient or animal to be treated as determined by the attending diagnostician. It is to be expected that the general end-use application dose range will be about 0.01 to 10 mg/kg per day for an effective therapeutic effect with 0.1 mg to 10 mg/kg per day being preferred.

15 The compounds of formula I which are useful as inhibitors of pepsin are represented by the structural formula Ip:



and the hydrates, isosteres or the pharmaceutically acceptable salts thereof wherein

R is -OR<sup>1</sup> or -NR<sup>2</sup>R<sup>3</sup> wherein, R<sup>1</sup>, R<sup>2</sup>, and R<sup>3</sup> are each independently selected from hydrogen, a (C<sub>1</sub>-C<sub>6</sub>)alkyl group, (C<sub>2</sub>-C<sub>6</sub>)alkanoyl, phenyl, benzyl, benzoyl, cyclohexyl, cyclohexylmethyl or 2-pyridylmethyl with NH<sub>2</sub> or OH, benzyl, isovaleryl amino (Iva), isoamyl amino (Iaa), isopropyl amino, and 2-pyridylmethyl being preferred,

R<sub>1</sub> is -P<sub>2</sub>-P<sub>3</sub>-P<sub>4</sub> with

P<sub>2</sub> being selected from Groups E and F with Val being preferred,

25 P<sub>3</sub> is selected from Groups E and F with Val being preferred or is deleted, and

P<sub>4</sub> is selected from Group K, preferably Iva, and

R<sub>2</sub> is selected from a side chain of an amino acid of Groups E and F with the side chain of Leu being preferred.

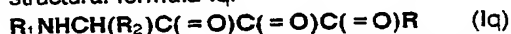
The preferred compounds are:

30 Iva-Val-Leu-C(O)C(O)Iva and

Iva-Val-Val-Leu-C(O)C(O)Iaa.

The compounds of formula (Ip) inhibit pepsin and therefore exert an antiulcer effect useful in the treatment and prevention of ulcers. For their end-use application, the potency and other biochemical parameters of the enzyme inhibiting characteristics of the compounds of (Ip) are readily ascertained by standard biochemical techniques well known in the art. Actual dose ranges for their specific end-use application will, of course, depend upon the nature and severity of the disease state of the patient or animal to be treated as determined by the attending diagnostician. It is to be expected that the general end-use application dose range will be about 0.01 to 10 mg/kg per day for an effective therapeutic effect with 0.1 mg to 10 mg/kg per day being preferred.

40 The compounds of formula I which are useful as inhibitors of Cathepsin D are represented by the structural formula Iq:



and the hydrates, isosteres or the pharmaceutically acceptable salts thereof, wherein

45 R is -OR<sup>1</sup> or -NR<sup>2</sup>R<sup>3</sup> wherein, R<sup>1</sup>, R<sup>2</sup>, and R<sup>3</sup> are each independently selected from hydrogen, a (C<sub>1</sub>-C<sub>6</sub>)alkyl group, (C<sub>2</sub>-C<sub>6</sub>)alkanoyl, phenyl, benzyl, benzoyl, cyclohexyl, cyclohexylmethyl or 2-pyridylmethyl with NH<sub>2</sub> or OH, benzyl, isovaleryl amino (Iva), isoamyl amino (Iaa), isopropyl amino, isobutyl amino and 2-pyridylmethyl being preferred,

R<sub>1</sub> is -P<sub>2</sub>-P<sub>3</sub>-P<sub>4</sub> with

P<sub>2</sub> being selected from Groups E and F, with Val or Ala being preferred,

50 P<sub>3</sub> is selected from Groups E and F or is deleted with Val being preferred, and

P<sub>4</sub> is selected from Group K with Cbz being preferred, and

R<sub>2</sub> is selected from a side chain of an amino acid of Groups E and F, with the side chain of Phe being preferred.

The preferred compounds are:

55 Cbz-Val-Val-Phe-C(O)C(O)Iva,

Iva-Val-Ala-Phe-C(O)C(O)NHCH<sub>2</sub>CH(CH<sub>3</sub>)<sub>2</sub>,

Iva-Val-Ala-Phe-C(O)C(O)Iva and

Iva-Val-Phe-C(O)C(O)OCH<sub>3</sub>.

As inhibitors of Cathepsin D the compounds of formula (Iq) are useful for the same end-use applications set forth for human leukocyte elastase inhibitors (Ia) and are also useful as antidemyelinating agents useful to prevent and arrest nerve tissue damage. For their end-use application, the potency and other biochemical parameters of the enzyme inhibiting characteristics of the compounds of (Iq) are readily ascertained by standard biochemical techniques well known in the art. Actual dose ranges for their specific end-use application will, of course, depend upon the nature and severity of the disease state of the patient or animal to be treated as determined by the attending diagnostician. It is to be expected that the general end-use application dose range will be about 0.01 to 10 mg/kg per day for an effective therapeutic effect with 0.1 mg to 10 mg/kg per day being preferred.

The compounds of formula I which are useful as inhibitors of angiotensin converting enzyme (ACE) are represented by the structural formula Ir:



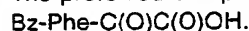
and the hydrates, isosteres or the pharmaceutically acceptable salts thereof, wherein

R is -OR<sup>1</sup> or -NR<sup>2</sup>R<sup>3</sup> wherein, R<sup>1</sup>, R<sup>2</sup>, and R<sup>3</sup> are each independently selected from hydrogen, a (C<sub>1</sub>-C<sub>6</sub>)alkyl group, (C<sub>2</sub>-C<sub>6</sub>)alkanoyl, phenyl, benzyl, benzoyl, cyclohexyl, cyclohexylmethyl or 2-pyridylmethyl with NH<sub>2</sub> or OH being preferred,

R<sub>1</sub> is selected from Group K with Bz being preferred, and

R<sub>2</sub> is selected from a side chain of an amino acid of Groups E, F and G with the side chain of Phe being preferred.

The preferred compounds is:



The compounds of formula (Ir) inhibit ACE and are therefore useful as antihypertensives for treating hypertension. For their end-use application, the potency and other biochemical parameters of the enzyme inhibiting characteristics of the compounds of (Ir) are readily ascertained by standard biochemical techniques well known in the art. Actual dose ranges for their specific end-use application will, of course, depend upon the nature and severity of the disease state of the patient or animal to be treated as determined by the attending diagnostician. It is to be expected that the general end-use application dose range will be about 0.01 to 10 mg/kg per day for an effective therapeutic effect with 0.1 mg to 10 mg/kg per day being preferred.

The compounds of formula I which are useful as inhibitors of enkephalinase are represented by the structural formula Is:



and the hydrates, isosteres or the pharmaceutically acceptable salts thereof, wherein

R is -OR<sup>1</sup> or -NR<sup>2</sup>R<sup>3</sup> wherein, R<sup>1</sup>, R<sup>2</sup>, and R<sup>3</sup> are each independently selected from hydrogen, a (C<sub>1</sub>-C<sub>6</sub>)alkyl group, (C<sub>2</sub>-C<sub>6</sub>)alkanoyl, phenyl, benzyl, benzoylcyclohexyl, cyclohexylmethyl, or 2-pyridylmethyl with NH<sub>2</sub> or OH being preferred,

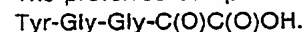
R<sub>1</sub> generically is -P<sub>2</sub>-P<sub>3</sub>, with

P<sub>2</sub> being Gly and

P<sub>3</sub> being selected from Group F or is deleted with Tyr being preferred, and

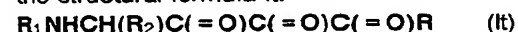
R<sub>2</sub> is hydrogen.

The preferred compound is:



The compounds of formula (Is) inhibit enkephalinase and therefore are useful as analgesics. For their end-use application, the potency and other biochemical parameters of the enzyme inhibiting characteristics of the compounds of (Is) are readily ascertained by standard biochemical techniques well known in the art. Actual dose ranges for their specific end-use application will, of course, depend upon the nature and severity of the disease state of the patient or animal to be treated as determined by the attending diagnostician. It is to be expected that the general end-use application dose range will be about 0.01 to 10 mg/kg per day for an effective therapeutic effect with 0.1 mg to 10 mg/kg per day being preferred.

The compounds of formula I which are useful as inhibitors of pseudomonas elastase are represented by the structural formula It:



and the hydrates, isosteres or the pharmaceutically acceptable salts thereof, wherein

R is -OR<sup>1</sup> or -NR<sup>2</sup>R<sup>3</sup> wherein, R<sup>1</sup>, R<sup>2</sup>, and R<sup>3</sup> are each independently selected from hydrogen, a (C<sub>1</sub>-C<sub>6</sub>)alkyl group, (C<sub>2</sub>-C<sub>6</sub>)alkanoyl, phenyl, benzyl, benzoyl, cyclohexyl, cyclohexylmethyl or 2-pyridylmethyl with NH<sub>2</sub> or OH being preferred,

R<sub>1</sub> is -P<sub>2</sub>-P<sub>3</sub> with

P<sub>2</sub> being selected from Group E with Ala being preferred, and

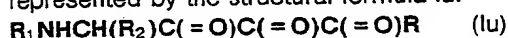
P<sub>3</sub> is selected from Group K with MeOSuc being preferred, and R<sub>2</sub> is selected from a side chain of an amino acid of Groups E and G with the side chain of Ala being preferred.

The preferred compound is

5 MeOSuc-Ala-Ala-C(O)C(O)NH<sub>2</sub>.

The compounds of formula (It) inhibit pseudomonas elastase and therefore are useful as antibacterial agents particularly useful against infections caused by pseudomonas bacteria. For their end-use application, the potency and other biochemical parameters of the enzyme inhibiting characteristics of the compounds of (It) are readily ascertained by standard biochemical techniques well known in the art. Actual dose ranges for  
10 their specific end-use application will, of course, depend upon the nature and severity of the disease state of the patient or animal to be treated as determined by the attending diagnostician. It is to be expected that the general end-use application dose range will be about 0.01 to 10 mg/kg per day for an effective therapeutic effect with 0.1 mg to 10 mg/kg per day being preferred.

The compounds of formula I which are useful as inhibitors of kallikreins, tissue or plasma, are  
15 represented by the structural formula lu:



and the hydrates, isosteres or the pharmaceutically acceptable salts thereof, wherein

R is -OR<sup>1</sup> or -NR<sup>2</sup>R<sup>3</sup> wherein, R<sup>1</sup>, R<sup>2</sup>, and R<sup>3</sup> are each independently selected from hydrogen, a (C<sub>1</sub>-C<sub>6</sub>)alkyl group, (C<sub>2</sub>-C<sub>6</sub>)alkanoyl, phenyl, benzyl, benzoyl, cyclohexyl, cyclohexylmethyl (CHM) or 2-pyridylmethyl  
20 with methyl, methoxy, NH<sub>2</sub> being preferred,

R<sub>1</sub> is -P<sub>2</sub>-P<sub>3</sub> with

P<sub>2</sub> being selected from Groups E and F with Phe being preferred,

P<sub>3</sub> being selected from Groups C, E and F, the residues of which may be in either the D- or L-configuration, and

25 R<sub>2</sub> is the side chain of an α-amino acid of Group A or is a member of Group J and preferably is the side chain of Arg or is (J-1).

The preferred compounds of this formula are:

pro-Phe-Arg-C(O)C(O)OCH<sub>3</sub>,

pro-Phe-Arg-C(O)C(O)NH<sub>2</sub>, and

30 pro-Phe-NHCH(J-1)-C(O)C(O)OCH<sub>3</sub>.

The compounds of formula (lu) are inhibitors of the kallikreins, tissue or plasma, and therefore inhibit kinin formations. Kinins, generally known to induce pain and vascular permeability associated with inflammation and infection, e.g., bacterial and viral. The inhibition of the kinin formation renders these compounds useful in the alleviation of pain and inflammation. Furthermore, these compounds are useful as  
35 male contraceptives in that they will dramatically interfere with normal sperm function. In their end-use application dose range will be about 0.01 to 10 mg/kg per day for an effective therapeutic effect with 0.1 mg to 10 mg/kg per day being preferred.

The compounds of Formula I which are of particular use as inhibitors of retroviral protease required for replication, particularly the HIV-1 and XIV-2 viral proteases, the viruses putatively responsible for causing  
40 AIDS (acquired immune deficiency syndrome) are those compounds of Formula Iv:



wherein

R is -OR<sup>1</sup> or -NR<sup>2</sup>R<sup>3</sup> wherein, R<sup>1</sup>, R<sup>2</sup>, and R<sup>3</sup> are each independently selected from hydrogen, a (C<sub>1</sub>-C<sub>6</sub>)alkyl group, (C<sub>2</sub>-C<sub>6</sub>)alkanoyl, phenyl, benzyl, benzoyl, cyclohexyl, cyclohexylmethyl (CHM) or 2-pyridylmethyl  
45 with methyl, methoxy, NH<sub>2</sub> and NHR<sup>3</sup> being preferred,

R<sub>1</sub> is -P<sub>2</sub>-P<sub>3</sub>-P<sub>4</sub> with

P<sub>2</sub> being selected from the Groups C, E, F and G, preferably Asn, Gln and Ala,

P<sub>3</sub> being selected from the Groups C, E, F and G, preferably Asn, Gln and Ala,

P<sub>4</sub> being selected from Group C, or being bAla or bVal, and preferably Ser or Thr, and optionally bearing  
50 an amino protecting group of Group K,

R<sub>2</sub> is the side chain of an α-amino acid of Groups F or E, or is cyclohexylmethyl (CHM) with the side chain of Met, Tyr, and Phe and CHM being preferred

The preferred compounds are:

Ser-Gln-Asn-Tyr-C(O)C(O)NH<sub>2</sub>,

55 Ser-Gln-Asn-Phe-C(O)C(O)NH(CHM),

Ser-Leu-Asn-Tyr-C(O)C(O)OH

Ser-Leu-Asn-Phe-C(O)C(O)OH,

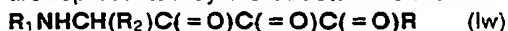
Thr-Gln-Asn-Tyr-C(O)C(O)NH(CHM),



- Thr-Gln-Asn-Phe-C(O)C(O)NH(CHM),  
 Thr-Gln-Asn-Met-C(O)C(O)NH(CHM),  
 Iva-Ser-Asn-Tyr-C(O)C(O)Iva,  
 Iva-Ser-Asn-Phe-C(O)C(O)Iva,  
 5 Ser-Gln-Asn-Met-C(O)C(O)NH(CHM),  
 Ser-Leu-Asn-Met-C(O)C(O)NH(CHM),  
 Thr-Gln-Asn-Met-C(O)C(O)NH(CHM),  
 Thr-Leu-Asn-Met-C(O)C(O)NH(CHM),  
 ) Cbz-Phe-C(O)C(O)OCH<sub>2</sub>Φ,  
 10 Cbz-Phe-C(O)C(O)OCH<sub>2</sub>Φ,  
 Tba-Phe-Nva-Cha-C(O)C(O)Iva,  
 H-Phe-Nva-Cha-C(O)C(O)Iva,  
 Iva-Tyr(Me)-Nva-Cha-C(O)C(O)Iva,  
 Boc-Phe-C(O)C(O)NH<sub>2</sub>,  
 15 Cbz-Phe-C(O)C(O)N(CH<sub>3</sub>)CH<sub>2</sub>C<sub>6</sub>H<sub>5</sub>, and  
 Cbz-Phe-C(O)C(O)OEt.

In their end-use application in the treatment of retroviral infections, the compounds of Formula (Iv) will be administered at about 1-100 mg per kg of body weight per day, preferably intravenously.

- The compounds of formula I which are useful as inhibitors of peptidyl-prolyl cis -trans isomerase (PPI) are represented by the structural formula Iw:



and the hydrates, isosteres or the pharmaceutically acceptable salts thereof wherein

- R is -OR<sup>1</sup> or -NR<sup>2</sup>R<sup>3</sup> wherein, R<sup>1</sup>, R<sup>2</sup>, and R<sup>3</sup> are each independently selected from hydrogen, a (C<sub>1</sub>-C<sub>6</sub>)alkyl group, (C<sub>2</sub>-C<sub>6</sub>)alkanoyl, phenyl, benzyl, benzoyl, cyclohexyl, cyclohexylmethyl, or 2- pyridylmethyl with  
 25 methyl, methoxy, NH<sub>2</sub> and NHR<sup>3</sup> being preferred,  
 R<sub>1</sub> is -P<sub>2</sub>-P<sub>3</sub> wherein

P<sub>2</sub> is selected from Group E with Ala being preferred,

P<sub>3</sub> is selected from Group K with MeOSuc being preferred, and

R<sub>2</sub> is selected from a side chain of an amino acid from Group E with the side chain of Ala being preferred.

- 30 The compounds of formula Iw are inhibitors of peptidylprolyl cis-trans isomerase and would therefore be expected to possess immunosuppressant activity. Immunosuppressants, like cyclosporin, can be used, for example, to lessen the rejection of transplanted tissue or organ by the immune system of the host.

- Having defined the scope of the compounds within the generic invention and within the individual subgeneric groups for each of the individual enzymes, the manner in which such may be prepared will be  
 35 described and illustrated.

In general, the compounds of formula I may be prepared using standard chemical reactions analogously known in the art. The procedure for preparing the formula I compounds is outlined in Scheme A wherein R, R<sub>1</sub>, and R<sub>2</sub> are as previously defined. Specifically, the compounds of formula 1 can be prepared by treatment of the appropriate ylide of formula 2 with (a) ozone and dimethyl sulfide or (b) singlet oxygen.

- 40 The ozonolysis reaction can be conveniently performed by, for example, bubbling an excess of ozone through a cooled solution of the appropriate formula 2 ylide. Suitable solvents include any nonreactive solvent in which the formula 2 ylide is soluble, for example, alkyl esters of simple alkanolic acids such as ethylacetate; the chlorinated hydrocarbons such as carbon tetrachloride, chloroform, 1,2-ethylenedichloride, 1,1,2,2-tetrachloroethane, and methylene chloride; the aromatic hydrocarbons such as benzene, toluene,  
 45 and xylene; a chlorinated aromatic such as 1,2,4-trichlorobenzene and o-dichlorobenzene; an alcohol such as methanol, ethanol, and isopropanol; or an ethereal solvent such as diethyl ether, tetrahydrofuran (THF), and p-dioxan. Methylene chloride is preferred.

- The temperature of the ozonolysis reaction mixture can be any temperature conducive to the reaction, typically from about -78° C to about 0° C, preferably from about -78° C to about -35° C, and most preferably  
 50 about -70° C. The time of the reaction will vary depending on the ylide, the concentration of the reactants, the temperature and other factors. Conveniently, ozone is bubbled into the reaction mixture until the solution turns blue indicating an excess of ozone.

- The ozonide is then treated with an excess of a reducing agent such as zinc metal or preferably dimethylsulfide. The desired formula 1 compound as the hydrate is isolated from the reaction mixture in  
 55 any convenient manner, typically by solvent removal (via evaporation). Purification may be accomplished by, for example, flash chromatography.

Oxidations utilizing singlet oxygen are well known. More specifically, singlet oxygen oxidation of an ylide to produce a tricarbonyl ester has been reported by H. Wasserman et al., J. Amer. Chem. Soc. 11 ,

371 (1989).

Singlet oxygen can be generated by dye-sensitized excitation of oxygen. Suitable dyes include Rose Bengal, Eosin Y and methylene blue. Other sensitizers include dinaphthalenethiophene. Typically Rose Bengal and Eosin Y are attached to a basic anion-exchange resin and methylene blue is attached to an acidic cation-exchange resin. Excitation is accomplished with a UV lamp such as a tungsten-iodine lamp. Suitable solvents are any solvents which promote and do not interfere with the desired reaction. Such solvents include the aromatic hydrocarbons such as benzene and toluene; hydrocarbons such as hexane; ethereal solvents such as diethyl ether, tetrahydrofuran (THF) p-dioxan; chlorinated hydrocarbons such as dichloromethane and chloroform; carbondisulfide; and alcohols such as methanol, ethanol, propanol, isopropanol and t-butyl-alcohol. Mixtures are operable. The temperature of the reaction mixture can be any suitable temperature from about -78° C to about 30° C typically from about -78° C to about -50° C. The time of the reaction will vary depending on the reactant, the solvent, concentrations, and temperature and can be from about 1 min to about 2 hours. Purification and isolation can be by those methods described above for specification and isolation of product from the ozonolysis reaction mixture.

The formula 2 ylide is prepared from the appropriate N-protected ylide, preferably from the phthaloyl protected ylide of formula 3. The removal of the phthaloyl group can be readily achieved by methods generally known to those skilled in the art. For example, a solution of the phthaloyl ylide can be allowed to react with hydrazine hydrate, typically about a 20-fold excess of hydrazine hydrate, until the reaction is substantially complete. The solvent can be any of those described above for the ozonolysis reaction and preferably will be an alcohol solvent such as EtOH. The temperature of the reaction mixture can be from about 0° C to about 60° C, conveniently at about room temperature, i.e., 25° C. The reaction time will vary depending on the specific reactant, the temperature, the solvent, and other factors known to influence reaction time. Conveniently the progress of the reaction can be monitored by thin layer chromatography (TLC).

Subsequent to removal of the phthaloyl group, the R<sub>1</sub> group can be linked to the now free amino group. When R<sub>1</sub> is an amino acid, protected amino acid or a peptide comprised of a number of amino acids optionally bearing an amino protecting group, the R<sub>1</sub> group can be linked to the unprotected, free amino compound by well known peptide coupling techniques.

In coupling individual amino acids or peptides to the deprotected formula 3 compound, appropriate side chain protecting groups are employed. The selection and use of an appropriate protecting group for these side chain functionalities is within the ability of those skilled in the art and will depend upon the amino acid to be protected and the presence of other protected amino acid residues in the peptide. The selection of such a side chain protecting group is critical in that it must not be removed during the deprotection and coupling steps of the synthesis. For example, when Boc is used as the  $\alpha$ -amino protecting group, the following side chain protecting groups are suitable: p-toluenesulfonyl (tosyl) moieties can be used to protect the amino side chains of amino acids such as Lys and Arg; p-methylbenzyl, acetamidomethyl, benzyl (Bzl), or t-butylsulfonyl moieties can be used to protect the sulfide containing side chains of amino acids such as cysteine, homocysteine, penicillamine and the like or derivatives thereof; benzyl (Bzl) or cyclohexyl ester moieties can be used to protect carboxylic acid side chains of amino acids such as Asp, Glu; a benzyl (Bzl) ether can be used to protect the hydroxy containing side chains of amino acids such as Ser and Thr; and a 2-bromocarbobenzoxy (Z(Br)) moiety can be used to protect the hydroxy containing side chains of amino acids such as Tyr. These side chain protecting groups are added and removed according to standard practices and procedures well known in the art. It is preferred to deprotect these side chain protecting groups with a solution of anisole in anhydrous hydrogen fluoride (1:10). Typically, deprotection of side chain protecting groups is performed after the peptide chain synthesis is complete but these groups can alternatively be removed at any other appropriate time. It is preferred to deprotect these side chains at the same time as the peptide is cleaved from the resin when solid phase synthetic methods are employed.

The phthaloyl(Pht)ylide of formula 3 is prepared by reaction of the phthaloyl protected acid chloride of formula 4 with the phosphonium ylide of formula 5. This reaction is performed by adding a solution of the appropriate formula 5 ylide, preferably dropwise, to a solution of the formula 4 acid chloride. Suitable solvents include those listed above for the ozonolysis reaction and will preferably be an ethereal solvent such as THF. The reaction will require from about 30 minutes to about 12 hours, typically about 2 to 3 hours, depending on the acid chloride, the ylide, the solvent(s), and the temperature which can be from about 0° C to about 60° C, conveniently at about room temperature, i.e., 25° C. Isolation and purification is accomplished by filtering the reaction mixture to remove solid products and subsequently chromatographing the filtrate, for example, on silica gel eluting with a 50% mixture of ethyl acetate and hexane.

The formula 5 phosphonium ylide, Wittig reagent, is prepared from the corresponding formula 6  $\alpha$ -

halocarboxylic acid derivative in the usual manner, that is, by reacting the  $\alpha$ -halo ester with a tertiary phosphine such as triphenylphosphine to yield a phosphonium salt. When treated with a strong base such as an organolithium compound, for example, lithium diisopropylamide (LDA), sodium hydride, or sodium amide, the acidic proton is removed and the desired ylide is formed.

5 Suitable solvents used in forming the Wittig reagent include any nonreactive solvent, for example, the aromatic hydrocarbons such as benzene or toluene, the chlorinated hydrocarbons such as carbon tetrachloride, chloroform, or methylene chloride, or the ethereal solvents such as diethyl ether or THF.

The reaction can conveniently be performed at from about 0°C to about 60°C, typically at room temperature, that is about 25°C. The halo group of the  $\alpha$ -halo ester is preferably a bromo group, but can be  
10 a chloro or iodo group or can be any good leaving group which forms a stable phosphonium salt such as a mesylate or tosylate group.

The acid chloride of formula 4 is prepared from the corresponding acid of formula 7 by, for example, reacting the acid with refluxing  $\alpha,\alpha$ -dichloromethyl methylether. After about 3 hours, the solution is allowed to cool and the product concentrated by solvent evaporation. The resulting crude acid chloride can be used  
15 directly without further purification in the reaction with the formula 5 phosphine.

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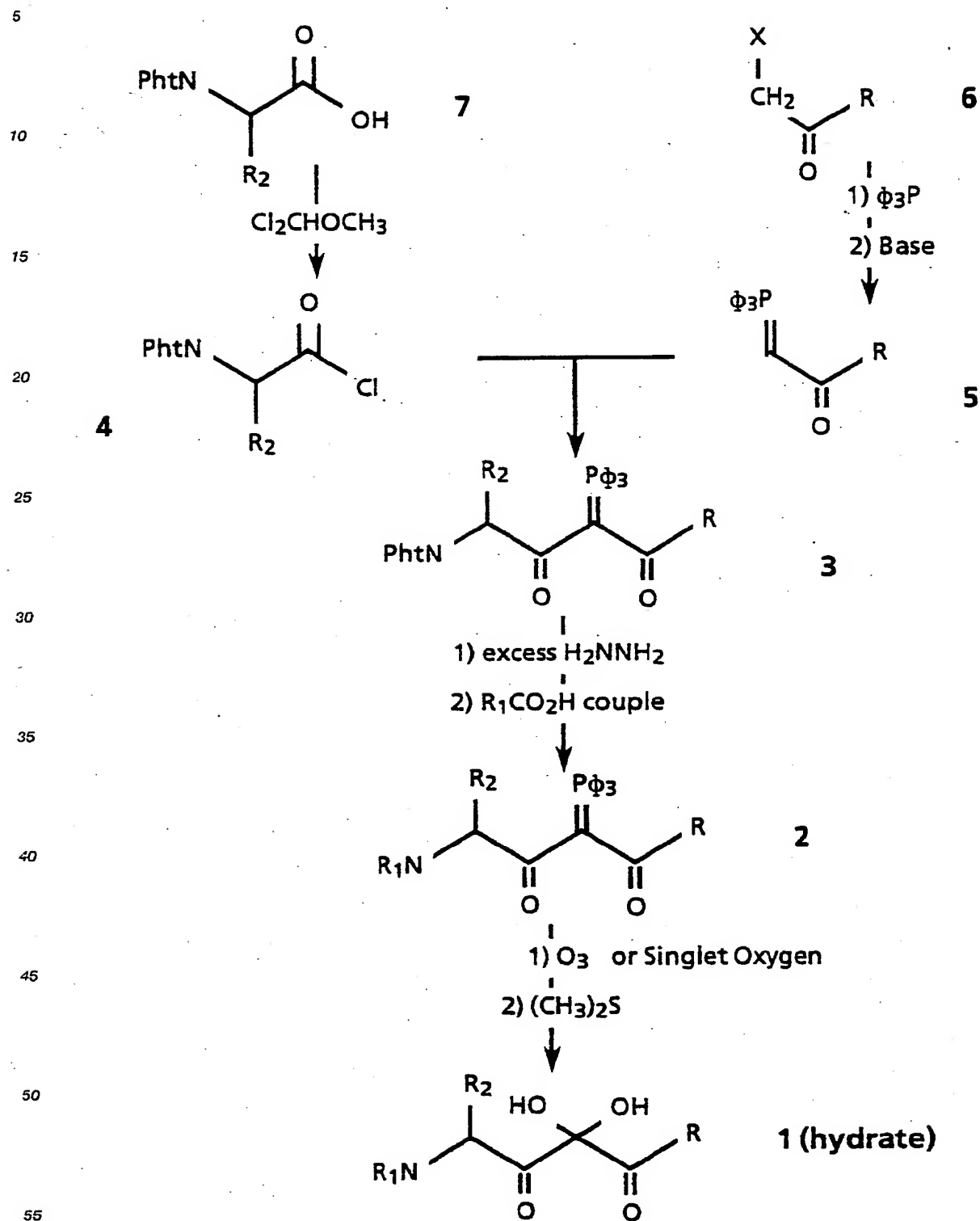
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Reaction Scheme A

The following specific examples are given to illustrate the preparation of this invention although the scope of compounds is not meant to be limiting to the scope of compounds embraced by formula I.

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**EXAMPLE 1**

10 PREPARATION OF (S)- $\alpha,\alpha$ -DIHYDROXY- $\beta$ -OXO- $\gamma$ -[[[(PHENYLMETHOXY)CARBONYL]AMINO]-  
BENZENEPENTANOIC ACID (Cbz-Phe-C(OH)<sub>2</sub>-CO<sub>2</sub>Et)

15 A. Preparation of (S)-1,3-dihydro- $\beta$ ,1,3-trioxo- $\gamma$ -(phenylmethyl)- $\alpha$ -(triphenylphosphoranylidene)-2H-isoindole-  
2-butanoic acid ethyl ester (Pht-Phe-C(P $\Phi$ <sub>3</sub>)-CO<sub>2</sub>Et)

Procedure: To a 25 ml round-bottomed flask under argon atmosphere was added 800 mg (2.76 mmol) of N-phthaloyl-L-phenylalanine and 4 ml of  $\alpha,\alpha$ -dichloromethyl methyl ether. The solution was heated at  
20 reflux for 3 hours. The cooled solution was concentrated to give 850 mg of a solid. This crude acid chloride was dissolved in 5 ml of dry THF and a solution of 1.74 g (5.0 mmol) of carbethoxymethylidenetriphenylphosphorane in 5 ml THF over 5 min. at 25 °C. A precipitate formed. After stirring for 2 hours, the mixture was filtered and the filtrate chromatographed in 150 g silica gel with 50% EtOAc/hexane. The desired fractions were combined to yield 1.31 g (2.09 mmol) of a colorless foam (76% yield). <sup>1</sup>H-NMR (CDCl<sub>3</sub>)  $\delta$   
25 7.5-7.7 (m,8H), 7.3-7.5 (m,17H), 7.12 (t,2H,J=6Hz), 7.03 (t,1H,J=6Hz), 6.28 (dd,1H, J<sub>a</sub>=10Hz, J<sub>b</sub>=4 Hz), 3.90 (m,2H), 3.75 (m,2H), 0.60 (t,3H,J=7Hz).

30 B. Preparation of (S)- $\beta$ -oxo- $\gamma$ -[[[(phenylmethoxy)carbonyl]amino]- $\alpha$ -(triphenylphosphoranylidene)-  
benzenepentanoic acid ethyl ester (Cbz-Phe-C(P $\Phi$ <sub>3</sub>)CO<sub>2</sub>Et)

A solution of 313 mg (0.50 mmol) phthaloyl ylide from Part A in 3 ml anhydrous ethyl alcohol was treated with 500 mg (10 mmol) hydrazine hydrate at 25 °C under nitrogen atmosphere. After 1 hour, no starting material was detected by TLC analysis. The volatiles were removed *in vacuo*. The residue was  
35 triturated with CHCl<sub>3</sub> and filtered. The filtrate was washed repeatedly with H<sub>2</sub>O, dried over MgSO<sub>4</sub>, and concentrated to a foam. The crude amine was dissolved in 3 ml CH<sub>2</sub>Cl<sub>2</sub> and 10 drops of pyridine. A solution of 90 mg (0.5 mmol) benzyl chloroformate in 1 ml CH<sub>2</sub>Cl<sub>2</sub> was added. After stirring for 30 minutes at 25 °C, the solution was poured into H<sub>2</sub>O and extracted with CH<sub>2</sub>Cl<sub>2</sub>. The organic extract was washed well with H<sub>2</sub>O, dried over MgSO<sub>4</sub>, concentrated, and flash chromatographed to give 245 mg (0.39 mmol, 78%  
40 yield) of a colorless glass. <sup>1</sup>H-NMR (CDCl<sub>3</sub>)  $\delta$  7.4-7.8 (m,15H), 7.15-7.35 (m,10H), 5.87 (m,1H), 5.61 (d,1H,J=7 Hz), 5.03 (d,1H,J=12 Hz), 4.96 (d,1H,J=12Hz), 3.7-3.9 (m,2H), 3.41 (dd,1H,J<sub>a</sub>=14 Hz,J<sub>b</sub>=4 Hz), 2.85 (dd,1H,J<sub>a</sub>=14 Hz, J<sub>b</sub>=8 Hz), 0.72 (t,3H,J=7 Hz).

45 C. Preparation of (S)- $\alpha,\alpha$ -dihydroxy- $\beta$ -oxo- $\gamma$ -[[[(phenylmethoxy)carbonyl]amino]benzenepentanoic acid (Cbz-Phe-C(OH)<sub>2</sub>-CO<sub>2</sub>Et)

A solution of 100 mg of stabilized ylide from Part B was dissolved in 25 ml CH<sub>2</sub>Cl<sub>2</sub> at -70 °C and a stream of ozone was bubbled into the solution until it turned blue. 0.5 ml dimethyl sulfide was added. The  
50 solution was evaporated and flash chromatographed using 30% ethyl acetate in hexane to give 17 mg of a foam. <sup>1</sup>H-NMR (CDCl<sub>3</sub>)  $\delta$  7.1-7.4 (m,10H), 5.20 (bs,1H), 5.16 (d,1H,J=7Hz), 5.05 (m,1H), 5.01 (s,2H), 4.16 (m,2H), 3.25 (dd,1H,J<sub>a</sub>=14 Hz,J<sub>b</sub>=5 Hz), 2.96 (dd,1H,J<sub>a</sub>=14 Hz,J<sub>b</sub>=8 Hz), 1.75 (bs,1H), 1.22 (t,3H,J=7 Hz).

55

**EXAMPLE 2**

PREPARATION OF Cbz-Phe-C(OH)<sub>2</sub>-C(O)N(CH<sub>3</sub>)CH<sub>2</sub>C<sub>6</sub>H<sub>5</sub>5 A. Preparation of ClCH<sub>2</sub>C(O)N(CH<sub>3</sub>)CH<sub>2</sub>C<sub>6</sub>H<sub>5</sub>

To a stirred solution of 8 ml (0.1 mole) chloroacetyl chloride in 100 ml CH<sub>2</sub>Cl<sub>2</sub> at 0° C was added 25.7 (0.2 mol) benzylmethylamine via dropping funnel over 10 min. The mixture was stirred for 30 min., poured into H<sub>2</sub>O, extracted into CH<sub>2</sub>Cl<sub>2</sub>, and dried over MgSO<sub>4</sub>. Concentration gave 19.0 g (0.095 mole) of amide  
10 as a clear liquid.

B. Preparation of  $\Phi_3P$ -CH<sub>2</sub>C(O)N(CH<sub>3</sub>)CH<sub>2</sub>C<sub>6</sub>H<sub>5</sub>

To a stirred solution of 4.0 g (20 mmol) of crude amide chloride from 2A above in 15 mL dry THF was added 5.24 g (20 mmol) Ph<sub>3</sub>P and 500 mg NaI. The solution was stirred at 25° C for 18 hours. Cooling and dilution with hexane and filtration gave 6.85 g of a white hygroscopic powder. Material loss was due to  
15 hygroscopic nature of the compounds.

20 C. Preparation of PhtN-Phe-C(=P $\Phi_3$ )C(O)N(CH<sub>3</sub>)CH<sub>2</sub>C<sub>6</sub>H<sub>5</sub>

1.6 g (3.5 mmol) of phosphonium salt from 2B was stirred in 25 ML H<sub>2</sub>O and treated with 420 mg (7 mmol) of n-butyllithium. 1.15 g (3.5 mmol) acid chloride of PhtN-Phe in 10 ML CH<sub>2</sub>Cl<sub>2</sub> was added and the  
25 mixture was stirred vigorously for 15 min. TLC showed one major spot. The CH<sub>2</sub>Cl<sub>2</sub> layer was removed, concentrated, and flash chromatographed using 70% EtOAc/Hexane on 150 mL silica. Chromatographed yield was 1.75 g (ca.2.5 mmol), 71% yield.

30 D. Preparation of Cbz-Phe-C[=P $\Phi_3$ ]-C(O)N(CH<sub>3</sub>)CH<sub>2</sub>C<sub>6</sub>H<sub>5</sub>

1.45 g (ca 2.0 mmol) of phthalimide ylide from 2C was dissolved in 20 mL methanol and treated with 1.0 g (20 mmol) of hydrazine hydrate at 15° C for 45 minutes. The solution was concentrated *in vacuo* at 20° C to a gum. This material was taken up in CHCl<sub>3</sub>, washed with H<sub>2</sub>O, and stirred at 25° C until  
35 phthalhydrazide formation was complete. After 5 hours, the CHCl<sub>3</sub> was removed *in vacuo*. The residue was taken up in 25 ml methanol and heated at 50° C for 8 hours. At this time TLC showed cleavage complete with very little lactam formation. The mixture was concentrated, triturated with CHCl<sub>3</sub> and filtered. Concentration gave the crude amine as an oil which was dissolved in 10 mL CH<sub>2</sub>Cl<sub>2</sub>.

Cbz Coupling - Half of the crude amine in 5 mL CH<sub>2</sub>Cl<sub>2</sub> (~1.0 mmol) was stirred with 0.5 mL pyridine  
40 and 155 mL of benzylchloroformate at 25° C. After stirring for 30 minutes, the solution was diluted with 50 mL CH<sub>2</sub>Cl<sub>2</sub>, washed with 5% HCl solution, dried over MgSO<sub>4</sub> and concentrated to give 800 mg of a residue. Flash chromatography on 100 mL silica using 50→75% EtOAc/Hexane gave 550 mg of a light yellow foam. Yield is ~78%.

45 E. Preparation of Cbz-Phe-C(OH)<sub>2</sub>-C(O)N(CH<sub>3</sub>)CH<sub>2</sub>C<sub>6</sub>H<sub>5</sub>

220 mg (0.31 mmol) of ylide from 2D was dissolved in 8 mL CH<sub>2</sub>Cl<sub>2</sub>, cooled to -70° C, and treated with O<sub>3</sub> until a faint green color formed. 0.5 mL Me<sub>2</sub>S was added and the yellow solution was concentrated *in*  
50 *vacuo*. Flash chromatography on 50 g silica using 25→30% EtOAc/Hexane yielded the title compound

The foregoing describes in detail the generic and specific aspects of the scope of the invention as well as the manner of making and using the invention. In addition thereto, although such procedures are known in the art, references setting forth state of the art procedures by which the compounds may be evaluated for their biochemical effects are also included herein.

55 For example, human elastase is assayed *in vitro* using chromophoric peptides, succinylalanylalanylalanyl-p-nitroanilide (A1), methoxysuccinylalanylalanylprolylvalyl-p-nitroanilide (A2), and others, all of which are available commercially. The assay buffer, pH 8.0, and assay techniques are similar to those described by Lottenberg, et al. (A3, A4). Enzyme is purified from human sputum (A5), although

recently it has become commercially available. Kinetic characterization of immediate inhibitors is by means of the Dixon plot (A6), whereas the characterization of slow- and/or tight-binding inhibitors used data analysis techniques reviewed by Williams and Morrison (A7).

Similarly, the other proteases are assayed and effects of inhibitors are assessed *in vitro* by similar spectroscopic techniques: cathepsin G (A2); thrombin (A3); chymotrypsin (A8); trypsin (A9); plasmin (A3); Cl esterase (A10); urokinase (A3); plasminogen activator (A11); acrosin (A12); beta-lactamase (A13); cathepsin B (A14); pepsin (A15); cathepsin D (A16) and leucine aminopeptidase (A17). *Pseudomonas* elastase was measured in a coupled assay procedure using a human elastase substrate and microsomal aminopeptidase.

Radiometric assays of angiotensin I-converting enzyme and enkephalinase and their inhibitors were based on the procedure of Ryan (A18) and used tritiated substrates purchased from Ventrex Laboratories, Inc. Radioimmunoassay was used for studies with renin (A19). C3-convertase was measured as described by Tack, et al. (A20).

The individual assay references are elaborated upon by the following:

- A1. The synthesis and analytical use of a highly sensitive and convenient substrate of elastase. J. Bieth, B. Spiess and C.G. Wermuth, *Biochemical Medicine*, 11 (1974) 350-375.
- A2. Mapping the extended substrate binding site of cathepsin G and human leukocyte elastase. Studies with peptide substrates related to the alpha 1-protease inhibitor reactive site. K. Nakajima, J.C. Powers, B.M. Ashe and M. Zimmerman, *The Journal of Biological Chemistry*, 254 (1979) 4027-4032.
- A3. Assay of coagulation proteases using peptide chromogenic and fluorogenic substrates. R. Lottenberg, a. Christensen, C.M. Jackson and P.L. Coleman, in *Methods in Enzymology* (L. Lorand, ed), Academic Press, New York, 1979, vol. 80, pp. 341-361.
- A4. Solution composition dependent variation in extinction coefficients for p -nitroaniline. R. Lottenberg and C.M. Jackson, *Biochimica et Biophysica Acta*, 742 (1983) 558-564.
- A5. A rapid procedure for the large scale purification of elastase and cathepsin G from human sputum. R.R. Martodam, R.J. Baugh, D.Y. Twumasi and I.E. Liener, *Preparative Biochemistry*, 9 (1979) 15-31.
- A6. The determination of enzyme inhibitor constants. M. Dixon, *The Biochemical Journal*, 55 (1953) 170-171.
- A7. The kinetics of reversible tight-binding inhibition. J.W. Williams and J.F. Morrison, in *Methods in Enzymology* (D.L. Purich, ed), Academic Press, New York, 1979, vol. 63, pp. 437-467.
- A8. Two convenient spectrophotometric enzyme assays. A biochemistry experiment in kinetics. J.A. Hurlbut, T.N. Ball, H.C. Pound and J.L. Graves, *Journal of Chemical Education*, 50 (1973) 149-151.
- A9. The preparation and properties of two new chromogenic substrates of trypsin. B.F. Erlanger, N. Kokowsky and W. Cohen, *Archives of Biochemistry and Biophysics*, 95 (1961) 271-278.
- A10. The human complement system serine proteases C1r and C1s and their proenzymes. R.B. Sim, in *Methods in Enzymology* (L. Lorand, ed), Academic Press, New York, 1979, vol. 80, pp. 26-42.
- A11. Extrinsic plasminogen activator and urokinase. J.H. Verheijen, C. Kluft, G.T.G. Chang and E. Mullaart, in *Methods of Enzymatic Analysis* (H.U. Bergmeyer, J. Bergmeyer and M. Grassl, eds), Verlag Chemie, Weinheim, 1984, third edition, vol. 5, pp. 425-433.
- A12. Sperm acrosin. W. Mueller-Esterl and H. Fritz, in *Methods in Enzymology* (L. Lorand, ed), Academic Press, New York, 1979, vol. 80, pp. 621-632.
- A13. Novel method for detection of beta-lactamases by using a chromogenic cephalosporin substrate. C.H. O'Callaghan, A. Morris, S.M. Kirby and A.H. Shingler, *Antimicrobial Agents and Chemotherapy*, 1 (1972) 283-288.
- A14. Cathepsin B, cathepsin H, and cathepsin L. A.J. Barrett and H. Kirschke, in *Methods in Enzymology* (L. Lorand, ed), Academic Press, New York, 1979, vol. 80, pp. 535-561.
- A15. Pepsins, gastricsins and their zymogens. A.P. Ryle, in *Methods of Enzymatic Analysis* (H.U. Bergmeyer, J. Bergmeyer and M. Grassl, eds), Verlag Chemie, Weinheim, 1984, third edition, vol. 5, pp. 223-238.
- A16. Cathepsin D, cathepsin E. V. Turk, T. Lah and I. Kregar, in *Methods of Enzymatic Analysis* (H.U. Bergmeyer, J. Bergmeyer and M. Grassl, eds), Verlag Chemie, Weinheim, 1984, third edition, vol 5, pp. 211-222.
- A17. Amino acid arylamidase. J.C.M. Hafkenscheid, in *Methods of Enzymatic Analysis* (H.U. Bergmeyer, J. Bergmeyer and M. Grassl, eds), Verlag Chemie, Weinheim, 1984, third edition, vol. 5, pp. 11-15.
- A18. Angiotensin I converting enzyme (kininase II). J.W. Ryan, in *Methods of Enzymatic Analysis* (H.U. Bergmeyer, J. Bergmeyer and M. Grassl, eds), Verlag Chemie, Weinheim, 1984, third edition, vol. 5, pp. 20-34.
- A19. Renin. T. Inagami and M. Naruse, in *Methods of Enzymatic Analysis* (H.U. Bergmeyer, J. Bergmeyer and M. Grassl, eds), Verlag Chemie, Weinheim, 1984, third edition, vol. 5, pp. 249-258.

A20. The third, fourth, and fifth components of human complement: isolation and biochemical properties. B.F. Tack, J. Janatova, M.L. Thomas, R.A. Harrison and C.H. Hammer, in *Methods in Enzymology* (L. Lorand, ed), Academic Press, New York, 1979, vol. 870, pp. 64-101.

By following the techniques referenced above, as well as by utilization of other known techniques, as well as by comparison with compounds known to be useful for treatment of the above-mentioned disease states, it is believed that adequate material is available to enable one of ordinary skill in the art to practice the invention. Of course, in the end-use application of the compounds of this invention, the compounds are preferably formulated into suitable pharmaceutical preparations such as tablets, capsules or elixers, for oral administration or in sterile solutions or suspensions for parenteral administration. The compounds of this invention can be administered to patients (animals and human) in need of such treatment in a dosage range of 5 to 500 mg per patient generally given several times, thus giving a total daily dose of from 5 to 2000 mg per day. As stated above, the dose will vary depending on severity of disease, weight of patient and other factors which a person skilled in the art will recognize.

Typically the compounds described above are formulated into pharmaceutical compositions as discussed below.

About 10 to 500 mg of a compound or mixture of compounds of formula I or a physiologically acceptable salt is compounded with a physiologically acceptable vehicle, carrier, excipient, binder, preservative, stabilizer or flavor, in a unit dosage form as called for by accepted pharmaceutical practice. The amount of active substance in these compositions or preparations is such that a suitable dosage in the range indicated is obtained.

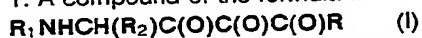
Illustrative of the adjuvants which may be incorporated in tablets, capsules and the like are the following: a binder such as gum tragacanth, acacia, corn starch or gelatin; an excipient such as microcrystalline cellulose; a disintegrating agent such as corn starch, pregelatinized starch or alginic acid; a lubricant such as magnesium stearate; a sweetening agent such as sucrose, lactose or Saccharin; a flavoring agent such as peppermint, oil of wintergreen or cherry. When the dosage unit form is a capsule, it may contain in addition to materials of the above type, a liquid carrier such as fatty oil. Various other materials may present as coatings or to otherwise modify the physical form of the dosage unit. For instance, tablets may be coated with shellac, sugar or both. A syrup or elixir may contain the active compound, sucrose as a sweetening agent, methyl and propyl paraben<sup>®</sup>s as preservatives, a dye and a flavoring such as cherry or orange flavor.

Sterile compositions for injection can be formulated according to conventional pharmaceutical practice by dissolving or suspending the active substance in a vehicle such as water for injection, a naturally occurring vegetable oil like sesame oil, coconut oil, peanut oil or cottonseed oil, or a synthetic fatty vehicle like ethyl oleate. Buffers, preservatives or antioxidants can be incorporated as required.

While the invention has been described in connection with specific embodiments thereof, it will be understood that it is capable of further modifications and this application is intended to cover any variations, uses, or adaptations of the invention following, in general, the principles of the invention and including such departures from the present disclosure as come within known or customary practice within the art to which the invention pertains and as may be applied to the essential features hereinbefore set forth, and as follows in the scope of the appended claims.

## Claims

1. A compound of the formula I:



the hydrates, isosteres or the pharmaceutically acceptable salts thereof wherein

R is -OR<sup>1</sup> or -NR<sup>2</sup>R<sup>3</sup> wherein, R<sup>1</sup>, R<sup>2</sup>, and R<sup>3</sup> are each independently selected from hydrogen, a (C<sub>1</sub>-C<sub>6</sub>)alkyl group, (C<sub>2</sub>C<sub>6</sub>)alkanoyl, phenyl, benzyl, benzoyl, cyclohexyl, cyclohexylmethyl or 2-pyridylmethyl,

R<sub>1</sub> is an amino protecting group selected from Group K, an α-amino acid or a peptide comprised of a number of α-amino acid building blocks, each of said α-amino acid or peptide optionally bearing an amino protecting group preferably selected from Group K,

R<sub>2</sub> is a side chain of an α-amino acid responsible for directing the inhibitor to the active site of the enzyme wherein the said α-amino acid and peptide moieties are building blocks selected from Groups A, B, C, D, E,

F, and G or wherein R<sub>2</sub> is a member of the Group J, and K is a terminal amino protecting group, members of these groups being

Group A: Lys and Arg

B: Glu, Asp



C: Ser, Thr, Gln, Asn, Cys, His, Ala (3pyr), Ala (4pyr) and N-methyl derivatives

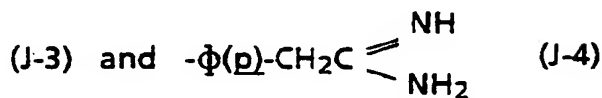
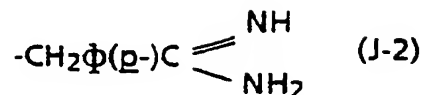
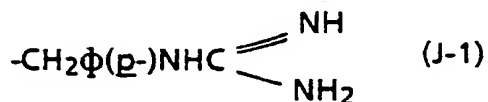
D: Pro, Ind

E: Ala, Leu, Ile, Val, Nva, Met, bVal, bAla, Nle and N-methyl derivatives

F: Phe, Tyr, Tyr(Me), Ala(3pyr), Ala(4pyr), Trp, Nal(1), and N-methyl derivatives

G: Gly, Sar

**J:**

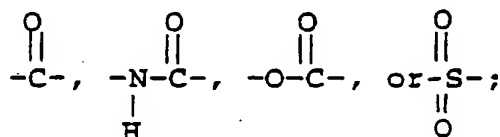


with  $\Phi$  representing phenyl,

K: Acetyl (Ac), Succinyl (Suc), Benzoyl (Bz), t-Butyloxycarbonyl (Boc) Carbobenzyloxy (Cbz), Tosyl (Ts), Dansyl (Dns), Isovaleryl (Iva), Methoxysuccinyl (MeOSuc), 1-Adamantanesulfonyl (AdSO<sub>2</sub>), 1-Adamantaneacetyl (AdAc), 2-Carboxybenzoyl (2CBz), Phenylacetyl (PhAc), t-Butylacetyl (Tba), bis [(1-naphthyl)-methyl]acetyl (BNMA),

or -A-R<sub>2</sub>, wherein

A is



and

R<sub>2</sub> is an aryl group containing 6, 10 or 12 carbons suitably substituted by 1 to 3 members selected independently from the group consisting of fluoro, chloro, bromo, iodo, trifluoromethyl, hydroxy, alkyl containing from 1 to 6 carbons, alkoxy containing from 1 to 6 carbons, carboxy, alkylcarbonylamino wherein the alkyl group contains 1 to 6 carbons, 5-tetrazoly, and acylsulfonamido (i.e., acylaminosulfonyl and sulfonylaminocarbonyl "Sac") containing from 1 to 15 carbons, provided that when the acylsulfonamido contains an aryl the aryl may be further substituted by a member selected from fluoro, chloro, bromo, iodo and nitro; and such other terminal amino protecting groups which are functionally equivalent thereto.

2. A compound of claim 1 wherein

R is -OR<sup>1</sup> or -NR<sup>2</sup>R<sup>3</sup> wherein, R<sup>1</sup>, R<sup>2</sup>, and R<sup>3</sup> are each independently selected from hydrogen, a (C<sub>1</sub>-C<sub>6</sub>)alkyl group, (C<sub>2</sub>-C<sub>6</sub>)alkanoyl, phenyl, benzyl, benzoyl, cyclohexyl, cyclohexylmethyl or 2-pyridylmethyl,

$R_1$  is  $-P_2-P_3-P_4-P_5$  with

P<sub>2</sub> being an  $\alpha$ -amino acid selected from Groups D, E and F,

P<sub>3</sub> is an  $\alpha$ -amino acid of Group D and E, or is lysine,

P<sub>4</sub> is an  $\alpha$ -amino acid of Group E or is deleted,

$P_5$  is a member of Group K,

R<sub>2</sub> is a side chain of an amino acid of Groups E or G.

3. A compound of claim 2 selected from the group consisting of

MeOSuc-Ala-Ala-Pro-Val-C(O)C(O)NH<sub>2</sub>,

 $\text{AdSO}_2\text{-Lys(2CBz)-Pro-Val-C(O)C(O)NH}_2$ ,

Cbz-Val-Pro-Val-C(O)C(O)NH<sub>2</sub>.

 $\text{Cl}\Phi\text{SacBz-Val-Pro-Val-C(O)C(O)NH}_2$ , $\text{Br}\Phi\text{SacBz-Val-Pro-Val-C(O)C(O)NH}_2$ , and

$\phi$ SacBz-Val-Pro-Val-C(O)C(O)NH<sub>2</sub>, and  
tPht-Val-Pro-Val-C(O)C(O)NH<sub>2</sub>.

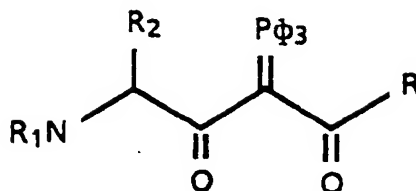
4. A compound of claim 1 wherein  
R is -OR<sup>1</sup> or -NR<sup>2</sup>R<sup>3</sup> wherein, R<sup>1</sup>, R<sup>2</sup>, and R<sup>3</sup> are each independently selected from hydrogen, a (C<sub>1</sub>-C<sub>6</sub>)alkyl  
group, (C<sub>2</sub>-C<sub>6</sub>)alkanoyl, phenyl, benzyl, benzoyl, cyclohexyl, cyclohexylmethyl or 2-pyridylmethyl,  
5 R<sub>1</sub> is -P<sub>2</sub>-P<sub>3</sub>-P<sub>4</sub>-P<sub>5</sub> with  
P<sub>2</sub> being selected from Groups D, E, and G,  
P<sub>3</sub> is selected from Groups E and G,  
P<sub>4</sub> is selected from Groups E and G or is deleted,  
10 P<sub>5</sub> is a member of Group K,  
R<sub>2</sub> is selected from a side chain of an amino acid of Groups E and F.
5. A compound of claim 4 selected from the group consisting of  
MeOSuc-Ala-Ala-Pro-Phe-C(O)C(O)OH,  
Suc-Ala-Ala-Pro-Phe-C(O)C(O)OH, and  
15 Cl $\phi$ SacBz-Val-Pro-Phe-C(O)C(O)OH.
6. A compound of claim 1 wherein  
R is -OR<sup>1</sup> or -NR<sup>2</sup>R<sup>3</sup> wherein, R<sup>1</sup>, R<sup>2</sup>, and R<sup>3</sup> are each independently selected from hydrogen, a (C<sub>1</sub>-C<sub>6</sub>)alkyl  
group, (C<sub>2</sub>-C<sub>6</sub>)alkanoyl, phenyl, benzyl, benzoyl, cyclohexyl, cyclohexylmethyl or 2-pyridylmethyl,  
R<sub>1</sub> is (a)-P<sub>2</sub>-P<sub>3</sub>, (b) -P<sub>2</sub> or (c) -P<sub>2</sub>-P<sub>3</sub>-P<sub>4</sub> wherein  
20 (a) P<sub>2</sub> is selected from Groups D, E and F,  
P<sub>3</sub> is selected from Group F, each P<sub>3</sub> being in the D-configuration,  
(b) P<sub>2</sub> is selected from Group K,  
(c) P<sub>2</sub> is selected from Group E,  
P<sub>3</sub> is selected from Groups C, G and E,  
25 P<sub>4</sub> is selected from Groups F, G and E or is deleted,  
R<sub>2</sub> is the arginine side chain, or is selected from a side chain of an amino acid of Group A or is a member  
of Group J.
7. A compound of claim 6 selected from the group consisting of  
phe-Pro-NHCH(J-I)-C(O)C(O)OH,  
30 phe-Pro-Arg-C(O)C(O)OH,  
Dns-Arg-C(O)C(O)OH,  
Phe-Ser-Ala-C(O)C(O)OH,  
phe-Pro-Lys-C(O)C(O)OH, and  
Bz-NHCH(J-I)-C(O)C(O)OH.
8. A compound of claim 1 wherein  
R is -OR<sup>1</sup> or -NR<sup>2</sup>R<sup>3</sup> wherein, R<sup>1</sup>, R<sup>2</sup>, and R<sup>3</sup> are each independently selected from hydrogen, a (C<sub>1</sub>-C<sub>6</sub>)alkyl  
group, (C<sub>2</sub>-C<sub>6</sub>)alkanoyl, phenyl, benzyl, benzoyl, cyclohexyl, cyclohexylmethyl or 2-pyridylmethyl,  
R<sub>1</sub> is -P<sub>2</sub>-P<sub>3</sub>-P<sub>4</sub>-P<sub>5</sub> with  
P<sub>2</sub> being selected from Groups D, E, G and K,  
40 P<sub>3</sub> is selected from Groups E, G and K or is deleted,  
P<sub>4</sub> is selected from Groups E, G and K or is deleted,  
P<sub>5</sub> is selected from Group K or is deleted, and  
R<sub>2</sub> is selected from a side chain of an amino acid of Groups E and F.
9. A compound of claim 1 selected from the group consisting of  
45 Bz-Phe-C(O)C(O)OCH<sub>3</sub>,  
Bz-Tyr-C(O)C(O)OCH<sub>3</sub>, and  
Ac-Leu-Phe-C(O)C(O)OCH<sub>3</sub>.
10. A compound of claim 1 wherein  
R<sub>2</sub> is the arginine side chain, or is selected from a side chain of an amino acid of Groups A and J,  
50 R<sub>1</sub> is selected from (a)-P<sub>2</sub>-P<sub>3</sub>, (b)-P<sub>2</sub> or (c)-P<sub>2</sub>-P<sub>3</sub>-P<sub>4</sub> with  
(a) P<sub>2</sub> is selected from Groups D, E or F, P<sub>3</sub> is selected from Group F, (each being in the D-  
configuration),  
(b) P<sub>2</sub> is selected from Group K,  
(c) P<sub>2</sub> is selected from Group D or E, P<sub>3</sub> is selected from Groups G and E, P<sub>4</sub> is selected from Groups G  
55 and E or is deleted.
11. A compound of claim 1 wherein  
R is -OR<sup>1</sup> or -NR<sup>2</sup>R<sup>3</sup> wherein, R<sup>1</sup>, R<sup>2</sup>, and R<sup>3</sup> are each independently selected from hydrogen, a (C<sub>1</sub>-C<sub>6</sub>)alkyl  
group, (C<sub>2</sub>-C<sub>6</sub>)alkanoyl, phenyl, benzyl, benzoyl, cyclohexyl, cyclohexylmethyl or 2-pyridylmethyl,

- $R_1$  is  $-P_2-P_3-P_4$  with  
 $P_2$  being selected from Group E and F,  
 $P_3$  is selected from Groups B, F and K, and  
 $P_4$  is selected from Group K,
- 5  $R_2$  is selected from a side chain of an amino acid of Group A or is a member of Group J.  
 12. A compound of claim 11 selected from the group consisting of  
 Dns-Glu-Phe-Lys-C(O)C(O)OCH<sub>3</sub>,  
 Ac-Ala-NHCH(J-1)-C(O)C(O)OCH<sub>3</sub>, and  
 Ac-Ala-Lys-C(O)C(O)OCH<sub>3</sub>.
- 10 13. A compound of claim 1 wherein  
 $R$  is  $-OR^1$  or  $-NR^2R^3$  wherein,  $R^1$ ,  $R^2$ , and  $R^3$  are each independently selected from hydrogen, a (C<sub>1</sub>-C<sub>6</sub>)alkyl  
 group, (C<sub>2</sub>-C<sub>6</sub>)alkanoyl, phenyl, benzyl, benzoyl, cyclohexyl, cyclohexylmethyl or 2-pyridylmethyl  
 $R_1$  is  $-P_2-P_3$  with  
 $P_2$  being selected from Groups E, G, D, C, F, A and B,
- 15  $P_3$  is selected from Group K,  
 $R_2$  is selected from a side chain of an amino acid of Group A or is a member of Group J.  
 14. A compound of claim 13 selected from the group consisting of  
 Cbz-Ala-Arg-C(O)C(O)NH<sub>2</sub>,  
 Ac-Ala-NHCH(J-1)-C(O)C(O)OCH<sub>3</sub>.
- 20 15. A compound of claim 1 wherein  
 $R$  is  $-OR^1$  or  $-NR^2R^3$  wherein,  $R^1$ ,  $R^2$ , and  $R^3$  are each independently selected from hydrogen, a (C<sub>1</sub>-C<sub>6</sub>)alkyl  
 group, (C<sub>2</sub>-C<sub>6</sub>)alkanoyl, phenyl, benzyl, benzoyl, cyclohexyl, cyclohexylmethyl or 2-pyridylmethyl,  
 $R_1$  is  $-P_2-P_3-P_4$  with  
 $P_2$  being selected from Groups E and F,
- 25  $P_3$  is selected from Groups E and F, and  
 $P_4$  is selected from Group K,  
 $R_2$  is selected from a side chain of an amino acid of Group A or is a member of Group J.  
 16. A compound of claim 15 which is  
 Bz-Leu-Ala-Arg-C(O)C(O)NH<sub>2</sub>.
- 30 17. A compound of claim 1 wherein  
 $R$  is  $-OR^1$  or  $-NR^2R^3$  wherein,  $R^1$ ,  $R^2$ , and  $R^3$  are each independently selected from hydrogen, a (C<sub>1</sub>-C<sub>6</sub>)alkyl  
 group, (C<sub>2</sub>-C<sub>6</sub>)alkanoyl, phenyl, benzyl, benzoyl, cyclohexyl, cyclohexylmethyl or 2-pyridylmethyl,  
 $R_1$  is  $-P_2-P_3$  with  
 $P_2$  being selected from Groups E and G,
- 35  $P_3$  is selected from Group B, and  
 $R_2$  is selected from a side chain of an amino acid of Group A or is a member of Group J.  
 18. A compound of claim 17 selected from the group consisting of  
 K-Glu-Gly-Arg-C(O)C(O)NH<sub>2</sub> and  
 K-Glu-Gly-Phe(Gua)-C(O)C(O)NH<sub>2</sub>.
- 40 19. A compound of claim 1 wherein  
 $R$  is  $-OR^1$  or  $-NR^2R^3$  wherein,  $R^1$ ,  $R^2$ , and  $R^3$  are each independently selected from hydrogen, a (C<sub>1</sub>-C<sub>6</sub>)alkyl  
 group, (C<sub>2</sub>-C<sub>6</sub>)alkanoyl, phenyl, benzyl, benzoyl, cyclohexyl, cyclohexylmethyl or 2-pyridylmethyl,  
 $R_1$  is  $-P_2-P_3-P_4$  with  
 $P_2$  is Gly,
- 45  $P_3$  is selected from Group B, and  
 $P_4$  is selected from Group K, and  
 $R_2$  is selected from a side chain of an  $\alpha$ -amino acid of Group A or is a member of Group J.  
 20. A compound of claim 19 selected from the group consisting of  
 Dns-Glu-Gly-Arg-C(O)C(O)NH<sub>2</sub> and
- 50 Dns-Glu-Gly-Phe(Gua)-C(O)C(O)NH<sub>2</sub>.  
 21. A compound of claim 1 wherein  
 $R$  is  $-OR^1$  or  $-NR^2R^3$  wherein,  $R^1$ ,  $R^2$ , and  $R^3$  are each independently selected from hydrogen, a (C<sub>1</sub>-C<sub>6</sub>)alkyl  
 group, (C<sub>2</sub>-C<sub>6</sub>)alkanoyl, phenyl, benzyl, benzoyl, cyclohexyl, cyclohexylmethyl or 2-pyridylmethyl,  
 $R_1$  is  $-P_2-P_3-P_4$  with
- 55  $P_2$  being selected from Group E and K,  
 $P_3$  is selected from Group E or is deleted,  
 $P_4$  is selected from Group K or is deleted,  
 $R_2$  is selected from a side chain of an amino acid of Group A or is a member of Group J.

22. A compound of claim 19 selected from the group consisting of  
 Boc-Leu-Leu-Arg-C(O)C(O)NH<sub>2</sub>,  
 Boc-Leu-Leu-Phe(Gua)-C(O)C(O)OCH<sub>3</sub>, and  
 Bz-NHCH(J-1)-C(O)C(O)NH<sub>2</sub>.
23. A compound of claim 1 wherein  
 R is -OR<sup>1</sup> or -NR<sup>2</sup>R<sup>3</sup> wherein, R<sup>1</sup>, R<sup>2</sup>, and R<sup>3</sup> are each independently selected from hydrogen, a (C<sub>1</sub>-C<sub>6</sub>)alkyl  
 group, (C<sub>2</sub>-C<sub>6</sub>)alkanoyl, phenyl, benzyl, benzoyl, cyclohexyl, cyclohexylmethyl or 2-pyridylmethyl,  
 R<sub>1</sub> is P<sub>2</sub>,  
 P<sub>2</sub> being selected from Group K, and  
 R<sub>2</sub> is selected from a side chain of an amino acid of Groups E, G and C.
24. A compound of claim 23 consisting of  
 $\Phi\text{CH}_2\text{CONHCH}_2\text{C(O)C(O)OCH}_3$ .
25. A compound of claim 1 wherein  
 R is -OR<sup>1</sup> or -NR<sup>2</sup>R<sup>3</sup> wherein, R<sup>1</sup>, R<sup>2</sup>, and R<sup>3</sup> are each independently selected from hydrogen, a (C<sub>1</sub>-C<sub>6</sub>)alkyl  
 group, (C<sub>2</sub>-C<sub>6</sub>)alkanoyl, phenyl, benzyl, benzoyl, cyclohexyl, cyclohexylmethyl or 2-pyridylmethyl  
 R<sub>1</sub> is P<sub>2</sub>-P<sub>3</sub> with  
 P<sub>2</sub> being Lys(Ac) or is selected from Groups E and C,  
 P<sub>3</sub> is selected from Group K, and  
 R<sub>2</sub> is a methyl group.
26. A compound of claim 25 which is  
 Ac-Lys-(Ac)-ala-C(O)C(O)OH.
27. A compound of claim 1 wherein  
 R is -OR<sup>1</sup> or -NR<sup>2</sup>R<sup>3</sup> wherein, R<sup>1</sup>, R<sup>2</sup>, and R<sup>3</sup> are each independently selected from hydrogen, a (C<sub>1</sub>-C<sub>6</sub>)alkyl  
 group, (C<sub>2</sub>-C<sub>6</sub>)alkanoyl, phenyl, benzyl, benzoyl, cyclohexyl, cyclohexylmethyl or 2-pyridylmethyl,
28. A compound of claim 27 selected from the group consisting of  
 Cbz-Phe-NHCH(J-1)-C(O)C(O)OCH<sub>3</sub>,  
 Ac-Leu-Leu-NHCH(J-1)-C(O)C(O)OH, and  
 Ac-Leu-Leu-Arg-C(O)C(O)OH.
29. A compound of Claim 1 wherein  
 R is -OR<sup>1</sup> or -NR<sup>2</sup>R<sup>3</sup> wherein, R<sup>1</sup>, R<sup>2</sup>, and R<sup>3</sup> are each independently selected from hydrogen, a (C<sub>1</sub>-C<sub>6</sub>)alkyl  
 group, (C<sub>2</sub>-C<sub>6</sub>)alkanoyl, phenyl, benzyl, benzoyl, cyclohexyl, cyclohexylmethyl, 2-pyridylmethyl or  
 isovaleryl amino (Iva),  
 R<sub>1</sub> is -P<sub>2</sub>-P<sub>3</sub>-P<sub>4</sub>-P<sub>5</sub>-P<sub>6</sub> wherein  
 P<sub>2</sub> is selected from Groups E, C, and F,  
 P<sub>3</sub> is selected from Groups E and F or is deleted,  
 P<sub>4</sub> is selected from Groups E, D, and F or is deleted,  
 P<sub>5</sub> is selected from Groups E, C, and F or is deleted,  
 P<sub>6</sub> is selected from Group K or when P<sub>4</sub> is bVal or bAla, P<sub>5</sub> and P<sub>6</sub> are deleted,  
 R<sub>2</sub> is selected from a side chain of an  $\alpha$ -amino acid of Groups E or F or is cyclohexylmethylene.
30. A compound of claim 29 selected from the group consisting of  
 Cbz-Nal(1)-His-Leu-C(O)C(O)OCH<sub>2</sub> $\Phi$ ,  
 Cbz-Phe-His-Leu-C(O)C(O)NHCH<sub>2</sub> $\Phi$ ,  
 Boc-Phe-Nva-Leu-C(O)C(O)NHCH<sub>2</sub> $\Phi$ ,  
 Cbz-Phe-Nva-Leu-C(O)C(O)NHCH<sub>2</sub> $\Phi$ ,  
 Boc-His-Pro-Phe-His-Leu-C(O)C(O)NHCH<sub>2</sub>(2-pyridyl),  
 Cbz-Phe-His-Cha-C(O)C(O)OCH<sub>2</sub> $\Phi$ ,  
 Cbz-His-Leu-C(O)C(O)NHCH<sub>2</sub> $\Phi$ ,  
 Boc-Phe-His-Leu-C(O)C(O)OCH<sub>2</sub> $\Phi$ ,  
 Boc-Phe-Nva-Cha-C(O)C(O)NHCH<sub>2</sub> $\Phi$ ,  
 Boc-Tyr(Me)-Nva-Cha-C(O)C(O)Iva,

- Boc-Phe-Ala(3pyr)-Cha-C(O)C(O)Iva,  
 Tba-Tyr(Me)-Nva-Cha-C(O)C(O)Iva,  
 Tba-Tyr(Me)-Ala(4pyr)-Cha-C(O)C(O)Iva,  
 bAla-Tyr(Me)-Nva-Cha-C(O)C(O)Iva,  
 5 bVal-Tyr(Me)-Nva-Cha-C(O)C(O)Iva,  
 bVal-Tyr(Me)-His-Cha-C(O)C(O)Iva, and  
 bAla-Tyr(Me)-His-Cha-C(O)C(O)Iva.
31. A compound of claim 1 wherein  
 R is -OR<sup>1</sup> or -NR<sup>2</sup>R<sup>3</sup> wherein, R<sup>1</sup>, R<sup>2</sup>, and R<sup>3</sup> are each independently selected from hydrogen, a (C<sub>1</sub>-C<sub>6</sub>)alkyl  
 10 group, (C<sub>2</sub>-C<sub>6</sub>)alkanoyl, phenyl, benzyl, benzoyl, cyclohexyl, cyclohexylmethyl, 2-pyridylmethyl or  
 isoamylamino (Iaa)  
 R<sub>1</sub> is -P<sub>2</sub>-P<sub>3</sub>-P<sub>4</sub> with  
 P<sub>2</sub> being selected from Groups E and F,  
 P<sub>3</sub> is selected from Groups E and F,  
 15 P<sub>4</sub> is selected from Group K,  
 R<sub>2</sub> is selected from a side chain of an amino acid of Groups E and F.
32. A compound of claim 31 selected from the group consisting of  
 Iva-Val-Leu-C(O)C(O)Iva and  
 Iva-Val-Val-Leu-C(O)C(O)Iaa.
- 20 33. A compound of claim 1 wherein  
 R is -OR<sup>1</sup> or -NR<sup>2</sup>R<sup>3</sup> wherein, R<sup>1</sup>, R<sup>2</sup>, and R<sup>3</sup> are each independently selected from hydrogen, a (C<sub>1</sub>-C<sub>6</sub>)alkyl  
 group, (C<sub>2</sub>-C<sub>6</sub>)alkanoyl, phenyl, benzyl, benzoyl, cyclohexyl, cyclohexylmethyl or 2-pyridylmethyl,  
 R<sub>1</sub> is -P<sub>2</sub>-P<sub>3</sub>-P<sub>4</sub> with  
 P<sub>2</sub> being selected from Groups E and F,  
 25 P<sub>3</sub> is selected from Groups E and F or is deleted,  
 P<sub>4</sub> is selected from Group K,  
 R<sub>2</sub> is selected from a side chain of an amino acid of Groups E and F.
34. A compound of claim 33 selected from the group consisting of  
 CBz-Val-Val-Phe-C(O)C(O)Iva,  
 30 Iva-Val-Ala-Phe-C(O)C(O)CH<sub>2</sub>CH(CH<sub>3</sub>)<sub>2</sub>,  
 Iva-Val-Phe-C(O)C(O)Iva, and  
 Iva-Val-Phe-C(O)C(O)OCH<sub>3</sub>.
35. A compound of claim 1 wherein  
 R is -OR<sup>1</sup> or -NR<sup>2</sup>R<sup>3</sup> wherein, R<sup>1</sup>, R<sup>2</sup>, and R<sup>3</sup> are each independently selected from hydrogen, a (C<sub>1</sub>-C<sub>6</sub>)alkyl  
 35 group, (C<sub>2</sub>-C<sub>6</sub>)alkanoyl, phenyl, benzyl, benzoyl, cyclohexyl, cyclohexylmethyl or 2-pyridylmethyl,  
 R<sub>1</sub> is selected from Group K,  
 R<sub>2</sub> is selected from a side chain of an amino acid of Groups E, F and G.
36. A compound of claim 35 consisting of  
 Bz-Phe-C(O)C(O)OH.
- 40 37. A compound of claim 1 wherein  
 R is -OR<sup>1</sup> or -NR<sup>2</sup>R<sup>3</sup> wherein, R<sup>1</sup>, R<sup>2</sup>, and R<sup>3</sup> are each independently selected from hydrogen, a (C<sub>1</sub>-C<sub>6</sub>)alkyl  
 group, (C<sub>2</sub>-C<sub>6</sub>)alkanoyl, phenyl, benzyl, benzoyl, cyclohexyl, cyclohexylmethyl or 2-pyridylmethyl,  
 R<sub>1</sub> is -P<sub>2</sub>-P<sub>3</sub> with  
 P<sub>2</sub> being Gly and  
 45 P<sub>3</sub> being selected from Group F or is deleted, and  
 R<sub>2</sub> is H.
38. A compound of claim 37 which is  
 Tyr-Gly-Gly-C(O)C(O)OH.
39. A compound of claim 1 wherein  
 50 R is -OR<sup>1</sup> or -NR<sup>2</sup>R<sup>3</sup> wherein, R<sup>1</sup>, R<sup>2</sup>, and R<sup>3</sup> are each independently selected from hydrogen, a (C<sub>1</sub>-C<sub>6</sub>)alkyl  
 group, (C<sub>2</sub>-C<sub>6</sub>)alkanoyl, phenyl, benzyl, benzoyl, cyclohexyl, cyclohexylmethyl or 2-pyridylmethyl,  
 R<sub>1</sub> is -P<sub>2</sub>-P<sub>3</sub> with  
 P<sub>2</sub> being selected from Group E,  
 P<sub>3</sub> is selected from Group K, and  
 55 R<sub>2</sub> is selected from a side chain of an amino acid of Groups E and G.
40. A compound of claim 39, said compound being MeOSuc-Ala-Ala-C(O)C(O)NH<sub>2</sub>.
41. A compound of claim 1 wherein  
 R is -OR<sup>1</sup> or -NR<sup>2</sup>R<sup>3</sup> wherein, R<sup>1</sup>, R<sup>2</sup>, and R<sup>3</sup> are each independently selected from hydrogen, a (C<sub>1</sub>-C<sub>6</sub>)alkyl

- group, (C<sub>2</sub>-C<sub>6</sub>)alkanoyl, phenyl, benzyl, benzoyl, cyclohexyl, cyclohexylmethyl or 2-pyridylmethyl,  
 R<sub>1</sub> is -P<sub>2</sub>-P<sub>3</sub> with  
 P<sub>2</sub> being selected from Groups E and F,  
 P<sub>3</sub> being selected from Groups C, E and F, the residues of which may be in either the D- or L-configuration,  
 5 and  
 R<sub>2</sub> is selected from a side chain of an amino acid of Group A or is a member of Group J.  
 42. A compound of claim 41 selected from the group consisting of  
 pro-Phe-Arg-C(O)C(O)OCH<sub>3</sub>,  
 pro-Phe-Arg-C(O)C(O)NH<sub>2</sub>, and  
 10 pro-Phe-NHCH(J-1)-C(O)C(O)OCH<sub>3</sub>.  
 43. A compound of claim 1 wherein  
 R is -OR<sup>1</sup> or -NR<sup>2</sup>R<sup>3</sup> wherein, R<sup>1</sup>, R<sup>2</sup>, and R<sup>3</sup> are each independently selected from hydrogen, a (C<sub>1</sub>-C<sub>6</sub>)alkyl  
 group, (C<sub>2</sub>-C<sub>6</sub>)alkanoyl, phenyl, benzyl, benzoyl, cyclohexyl, cyclohexylmethyl or 2-pyridylmethyl,  
 R<sub>1</sub> is -P<sub>2</sub>-P<sub>3</sub>-P<sub>4</sub> with  
 15 P<sub>2</sub> being selected from the Groups C, E, F and G,  
 P<sub>3</sub> being selected from the Groups C, E, F and G,  
 P<sub>4</sub> being selected from Group C, or being bAla or bVal, and optionally bearing an amino protecting group of  
 Group K,  
 R<sub>2</sub> is a side chain of an amino acid of Groups F and E, or is a cyclohexylmethyl (CHM) group.  
 20 44. A compound of claim 43 selected from the group consisting of  
 Ser-Gln-Asn-Tyr-C(O)C(O)NH<sub>2</sub>,  
 Ser-Gln-Asn-Phe-C(O)C(O)NH(CHM),  
 Ser-Leu-Asn-Tyr-C(O)C(O)OH,  
 Ser-Leu-Asn-Phe-C(O)C(O)OH,  
 25 Thr-Gln-Asn-Tyr-C(O)C(O)NH(CHM),  
 Thr-Gln-Asn-Phe-C(O)C(O)NH(CHM),  
 Thr-Gln-Asn-Met-C(O)C(O)NH(CHM),  
 Iva-Ser-Asn-Tyr-C(O)C(O)Iva,  
 Iva-Ser-Asn-Phe-C(O)C(O)Iva,  
 30 Ser-Gln-Asn-Met-C(O)C(O)NH(CHM),  
 Ser-Leu-Asn-Met-C(O)C(O)NH(CHM),  
 Thr-Gln-Asn-Met-C(O)C(O)NH(CHM),  
 Thr-Leu-Asn-Met-C(O)C(O)NH(CHM),  
 Cbz-Phe-C(O)C(O)OCH<sub>2</sub>Φ,  
 35 Cbz-Phe-C(O)C(O)OCH<sub>2</sub>Φ,  
 Tba-Phe-Nva-Cha-C(O)C(O)Iva,  
 H-Phe-Nva-Cha-C(O)C(O)Iva,  
 Iva-Tyr(Me)-Nva-Cha-C(O)C(O)Iva,  
 BOC-Phe-C(O)C(O)NH<sub>2</sub>,  
 40 Cbz-Phe-C(O)C(O)N(CH<sub>3</sub>)CH<sub>2</sub>C<sub>6</sub>H<sub>5</sub>, and  
 Cbz-Phe-C(O)C(O)OEt.  
 45. A compound of claim 1 wherein  
 R is -OR<sup>1</sup> or -NR<sup>2</sup>R<sup>3</sup> wherein, R<sup>1</sup>, R<sup>2</sup>, and R<sup>3</sup> are each independently selected from hydrogen, a (C<sub>1</sub>-C<sub>6</sub>)alkyl  
 group, (C<sub>2</sub>-C<sub>6</sub>)alkanoyl, phenyl, benzyl, benzoyl, cyclohexyl, cyclohexylmethyl or 2-pyridylmethyl,  
 45 R<sub>1</sub> is -P<sub>2</sub>-P<sub>3</sub> wherein  
 P<sub>2</sub> is selected from Group E,  
 P<sub>3</sub> is selected from Group K, and  
 R<sub>2</sub> is selected from a side chain of an amino acid from Group E.  
 46. A process for preparing a compound of the formula  
 50 **R<sub>1</sub>NHCH(R<sub>2</sub>)C(O)C(O)C(O)R**  
 wherein R, R<sub>1</sub> and R<sub>2</sub> are as defined in Claim 1 which comprises treating a solution of a compound of the  
 formula



with either a) singlet oxygen or b) excess ozone followed by dimethylsulfide, and isolating the product.

47. The compounds of claim 1 for use as a medicine.

48. The compounds of claim 1 for use as a pharmaceutically active substance.

49. The use of the compounds of claim 1 for the preparation of a pharmaceutical composition to inhibit peptidases and isomerases.

Claims for the following Contracting State: ES

1. A process for preparing a compound of the formula I:



the hydrates, isosteres or the pharmaceutically acceptable salts thereof wherein

R is  $-\text{OR}^1$  or  $-\text{NR}^2\text{R}^3$  wherein,  $\text{R}^1$ ,  $\text{R}^2$ , and  $\text{R}^3$  are each independently selected from hydrogen, a  $(\text{C}_1-\text{C}_6)$  alkyl group,  $(\text{C}_2-\text{C}_6)$  alkanoyl, phenyl, benzyl, benzoyl, cyclohexyl, cyclohexylmethyl or 2-pyridylmethyl,

$\text{R}_1$  is an amino protecting group selected from Group K, an  $\alpha$ -amino acid or a peptide comprised of a number of  $\alpha$ -amino acid building blocks, each of said  $\alpha$ -amino acid or peptide optionally bearing an amino protecting group preferably selected from Group K,

$\text{R}_2$  is a side chain of an  $\alpha$ -amino acid responsible for directing the inhibitor to the active site of the enzyme wherein the said  $\alpha$ -amino acid and peptide moieties are building blocks selected from Groups A, B, C, D, E, F, and G or wherein  $\text{R}_2$  is a member of the Group J, and K is a terminal amino protecting group, members of these groups being

Group A: Lys and Arg

Group B: Glu, Asp

Group C: Ser, Thr, Gln, Asn, Cys, His, Ala (3pyr), Ala (4pyr) and N-methyl derivatives

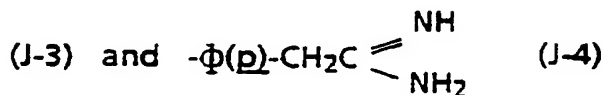
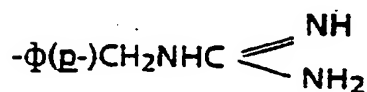
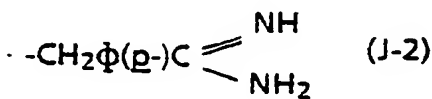
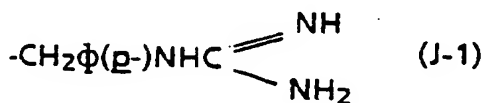
Group D: Pro, Ind

Group E: Ala, Leu, Ile, Val, Nva, Met, bVal, bAla, Nle and N-methyl derivatives

Group F: Phe, Tyr, Tyr(Me), Ala(3pyr), Ala(4pyr), Trp, Nal (1), and N-methyl derivatives

Group G: Gly, Sar

Group J:

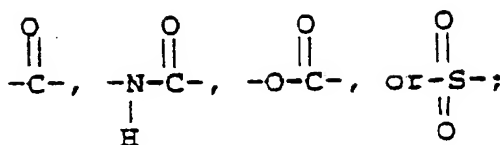


with  $\Phi$  representing phenyl,

K: Acetyl (Ac), Succinyl (Suc), Benzoyl (Bz), t-Butyloxycarbonyl (Boc), Carbobenzyloxy (Cbz), Tosyl (Ts), Dansyl (Dns), Isovaleryl (Iva), Methoxysuccinyl (MeOSuc), 1-Adamantanesulfonyl (AdSO<sub>2</sub>), 1-Adamantaneacetyl (AdAc), 2-Carboxybenzoyl (2CBz), Phenylacetyl (PhAc), t-Butylacetyl (Tba), bis [(1-naphthyl)-methyl]acetyl (BNMA),

or  $-\text{A-R}_2$  wherein

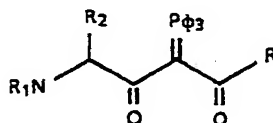
A is



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and  
 10  $R_2$  is an aryl group containing 6, 10 or 12 carbons suitably substituted by 1 to 3 members selected independently from the group consisting of fluoro, chloro, bromo, iodo, trifluoromethyl, hydroxy, alkyl containing from 1 to 6 carbons, alkoxy containing from 1 to 6 carbons, carboxy, alkylcarbonylamino wherein the alkyl group contains 1 to 6 carbons, 5-tetrazoly, and acylsulfonamido (i.e., acylaminosulfonyl and sulfonylamino carbonyl "Sac") containing from 1 to 15 carbons, provided that when the acylsulfonamido contains an aryl the aryl may be further substituted by a member selected from fluoro, chloro, bromo, iodo and nitro; and such other terminal amino protecting groups which are functionally equivalent thereto, process comprises treating a solution of a compound of the formula

20



- with either a) singlet oxygen or b) excess ozone followed by dimethylsulfide, and isolating the product.
- 25 2. The process of claim 1 wherein  
 R is  $-\text{OR}^1$  or  $-\text{NR}^2\text{R}^3$  wherein,  $\text{R}^1$ ,  $\text{R}^2$ , and  $\text{R}^3$  are each independently selected from hydrogen, a  $(\text{C}_1-\text{C}_6)$ alkyl group,  $(\text{C}_2-\text{C}_6)$ alkanoyl, phenyl, benzyl, benzoyl, cyclohexyl, cyclohexylmethyl or 2-pyridylmethyl,  
 $\text{R}_1$  is  $-\text{P}_2-\text{P}_3-\text{P}_4-\text{P}_5$  with  
 $\text{P}_2$  being an  $\alpha$ -amino acid selected from Groups D, E and F,  
 $\text{P}_3$  is an  $\alpha$ -amino acid of Group D and E, or is lysine,  
 30  $\text{P}_4$  is an  $\alpha$ -amino acid of Group E or is deleted,  
 $\text{P}_5$  is a member of Group K,  
 $\text{R}_2$  is a side chain of an amino acid of Groups E or G.
3. The process of claim 2 wherein the compound is selected from the group consisting of  
 35 MeOSuc-Ala-Ala-Pro-Val-C(O)C(O)NH<sub>2</sub>,  
 AdSO<sub>2</sub>-Lys(2CBz)-Pro-Val-C(O)C(O)NH<sub>2</sub>,  
 Cbz-Val-Pro-Val-C(O)C(O)NH<sub>2</sub>,  
 Cl $\phi$ SacBz-Val-Pro-Val-C(O)C(O)NH<sub>2</sub>,  
 Br $\phi$ SacBz-Val-Pro-Val-C(O)C(O)NH<sub>2</sub>,  
 40  $\phi$ SacBz-Val-Pro-Val-C(O)C(O)NH<sub>2</sub>, and  
 tPht-Val-Pro-Val-C(O)C(O)NH<sub>2</sub>.
4. The process of claim 1 wherein  
 R is  $-\text{OR}^1$  or  $-\text{NR}^2\text{R}^3$  wherein,  $\text{R}^1$ ,  $\text{R}^2$ , and  $\text{R}^3$  are each independently selected from hydrogen, a  $(\text{C}_1-\text{C}_6)$ alkyl group,  $(\text{C}_2-\text{C}_6)$ alkanoyl, phenyl, benzyl, benzoyl, cyclohexyl, cyclohexylmethyl or 2-pyridylmethyl,  
 $\text{R}_1$  is  $-\text{P}_2-\text{P}_3-\text{P}_4-\text{P}_5$  with  
 45  $\text{P}_2$  being selected from Groups D, E, and G,  
 $\text{P}_3$  is selected from Groups E and G,  
 $\text{P}_4$  is selected from Groups E and G or is deleted,  
 $\text{P}_5$  is a member of Group K,  
 $\text{R}_2$  is selected from a side chain of an amino acid of Groups E and F.
5. The process of claim 4 wherein the compound is selected from the group consisting of  
 50 MeOSuc-Ala-Ala-Pro-Phe-C(O)C(O)OH,  
 Suc-Ala-Ala-Pro-Phe-C(O)C(O)OH, and  
 Cl $\phi$ SacBz-Val-Pro-Phe-C(O)C(O)OH.
6. The process of claim 1 wherein  
 55 R is  $-\text{OR}^1$  or  $-\text{NR}^2\text{R}^3$  wherein,  $\text{R}^1$ ,  $\text{R}^2$ , and  $\text{R}^3$  are each independently selected from hydrogen, a  $(\text{C}_1-\text{C}_6)$ alkyl group,  $(\text{C}_2-\text{C}_6)$ alkanoyl, phenyl, benzyl, benzoyl, cyclohexyl, cyclohexylmethyl or 2-pyridylmethyl,  
 $\text{R}_1$  is (a)  $-\text{P}_2-\text{P}_3$ , (b)  $-\text{P}_2$  or (c)  $-\text{P}_2-\text{P}_3-\text{P}_4$  wherein



- (a)  $P_2$  is selected from Groups D, E and F,  
 $P_3$  is selected from Group F, each  $P_3$  being in the D-configuration,  
 (b)  $P_2$  is selected from Group K,  
 (c)  $P_2$  is selected from Group E.
- 5  $P_3$  is selected from Groups C, G and E.  
 $P_4$  is selected from Groups F, G and E or is deleted,  
 $R_2$  is the arginine side chain, or is selected from a side chain of an amino acid of Group A or is a member of Group J.
7. The process of claim 6 wherein the compound is selected from the group consisting of  
 10 phe-Pro-NHCH(J-I)-C(O)C(O)OH,  
 phe-Pro-Arg-C(O)C(O)OH,  
 Dns-Arg-C(O)C(O)OH,  
 Phe-Ser-Ala-C(O)C(O)OH,  
 phe-Pro-Lys-C(O)C(O)OH, and  
 15 Bz-NHCH(J-I)-C(O)C(O)OH.
8. The process of claim 1 wherein  
 $R$  is  $-OR^1$  or  $-NR^2R^3$  wherein,  $R^1$ ,  $R^2$ , and  $R^3$  are each independently selected from hydrogen, a  $(C_1-C_6)$ alkyl group,  $(C_2-C_6)$ alkanoyl, phenyl, benzyl, benzoyl, cyclohexyl, cyclohexylmethyl or 2-pyridylmethyl,  
 $R_1$  is  $-P_2-P_3-P_4-P_5$  with  
 20  $P_2$  being selected from Groups D, E, G and K,  
 $P_3$  is selected from Groups E, G and K or is deleted,  
 $P_4$  is selected from Groups E, G and K or is deleted,  
 $P_5$  is selected from Group K or is deleted, and  
 $R_2$  is selected from a side chain of an amino acid of Groups E and F.
- 25 9. A compound of claim 1 selected from the group consisting of  
 Bz-Phe-C(O)C(O)OCH<sub>3</sub>,  
 Bz-Tyr-C(O)C(O)OCH<sub>3</sub>, and  
 Ac-Leu-Phe-C(O)C(O)OCH<sub>3</sub>.
10. The process of claim 1 wherein  
 30  $R_2$  is the arginine side chain, or is selected from a side chain of an amino acid of Groups A and J,  
 $R_1$  is selected from (a)- $P_2-P_3$ , (b)- $P_2$  or (c)- $P_2-P_3-P_4$  with  
 (a)  $P_2$  is selected from Groups D, E or F,  $P_3$  is selected from Group F, (each being in the D-configuration),  
 (b)  $P_2$  is selected from Group K,  
 35 (c)  $P_2$  is selected from Group D or E,  $P_3$  is selected from Groups G and E,  $P_4$  is selected from Groups G and E or is deleted.
11. The process of claim 1 wherein  
 $R$  is  $-OR^1$  or  $-NR^2R^3$  wherein,  $R^1$ ,  $R^2$ , and  $R^3$  are each independently selected from hydrogen, a  $(C_1-C_6)$ alkyl group,  $(C_2-C_6)$ alkanoyl, phenyl, benzyl, benzoyl, cyclohexyl cyclohexylmethyl or 2-pyridylmethyl,  
 40  $R_1$  is  $P_2-P_3-P_4$  with  
 $P_2$  being selected from Group E and F,  
 $P_3$  is selected from Groups B, F and K, and  
 $P_4$  is selected from Group K,  
 $R_2$  is selected from a side chain of an amino acid of Group A or is a member of Group J.
- 45 12. The process of claim 11 wherein the compound is selected from the group consisting of  
 Dns-Glu-Phe-Lys-C(O)C(O)OCH<sub>3</sub>,  
 Ac-Ala-NHCH(J-1)-C(O)C(O)OCH<sub>3</sub>, and  
 Ac-Ala-Lys-C(O)C(O)OCH<sub>3</sub>.
13. The process of claim 1 wherein  
 50  $R$  is  $-OR^1$  or  $-NR^2R^3$  wherein,  $R^1$ ,  $R^2$ , and  $R^3$  are each independently selected from hydrogen, a  $(C_1-C_6)$ alkyl group,  $(C_2-C_6)$ alkanoyl, phenyl, benzyl, benzoyl, cyclohexyl, cyclohexylmethyl or 2-pyridylmethyl  
 $R_1$  is  $-P_2-P_3$  with  
 $P_2$  being selected from Groups E, G, D, C, F, A and B,  
 $P_3$  is selected from Group K,  
 55  $R_2$  is selected from a side chain of an amino acid of Group A or is a member of Group J.
14. The process of claim 13 wherein the compound is selected from the group consisting of  
 Cbz-Ala-Arg-C(O)C(O)NH<sub>2</sub>,  
 Ac-Ala-NHCH(J-1)-C(O)C(O)OCH<sub>3</sub>.

15. The process of claim 1 wherein  
 R is -OR<sup>1</sup> or -NR<sup>2</sup>R<sup>3</sup> wherein, R<sup>1</sup>, R<sup>2</sup>, and R<sup>3</sup> are each independently selected from hydrogen, a (C<sub>1</sub>-C<sub>6</sub>)alkyl group, (C<sub>2</sub>-C<sub>6</sub>)alkanoyl, phenyl, benzyl, benzoyl, cyclohexyl, cyclohexylmethyl or 2-pyridylmethyl,  
 R<sub>1</sub> is -P<sub>2</sub>-P<sub>3</sub>-P<sub>4</sub> with  
 5 P<sub>2</sub> being selected from Groups E and F,  
 P<sub>3</sub> is selected from Groups E and F, and  
 P<sub>4</sub> is selected from Group K,  
 R<sub>2</sub> is selected from a side chain of an amino acid of Group A or is a member of Group J.
16. The process of claim 15 wherein the compound is  
 10 Bz-Leu-Ala-Arg-C(O)C(O)NH<sub>2</sub>.
17. The process of claim 1 wherein  
 R is -OR<sup>1</sup> or -NR<sup>2</sup>R<sup>3</sup> wherein, R<sup>1</sup>, R<sup>2</sup>, and R<sup>3</sup> are each independently selected from hydrogen, a (C<sub>1</sub>-C<sub>6</sub>)alkyl group (C<sub>2</sub>-C<sub>6</sub>)alkanoyl, phenyl, benzyl, benzoyl, cyclohexyl, cyclohexylmethyl or 2-pyridylmethyl,  
 R<sub>1</sub> is -P<sub>2</sub>-P<sub>3</sub> with  
 15 P<sub>2</sub> being selected from Groups E and G,  
 P<sub>3</sub> is selected from Group B, and  
 R<sub>2</sub> is selected from a side chain of an amino acid of Group A or is a member of Group J.
18. The process of claim 17 wherein the compound is selected from the group consisting of  
 K-Glu-Gly-Arg-C(O)C(O)NH<sub>2</sub> and  
 20 K-Glu-Gly-Phe(Gua)-C(O)C(O)NH<sub>2</sub>.
19. The process of claim 1 wherein  
 R is -OR<sup>1</sup> or -NR<sup>2</sup>R<sup>3</sup> wherein, R<sup>1</sup>, R<sup>2</sup>, and R<sup>3</sup> are each independently selected from hydrogen, a (C<sub>1</sub>-C<sub>6</sub>)alkyl group, (C<sub>2</sub>-C<sub>6</sub>)alkanoyl, phenyl, benzyl, benzoyl, cyclohexyl, cyclohexylmethyl or 2-pyridylmethyl,  
 R<sub>1</sub> is -P<sub>2</sub>-P<sub>3</sub>-P<sub>4</sub> with  
 25 P<sub>2</sub> is Gly,  
 P<sub>3</sub> is selected from Group B, and  
 P<sub>4</sub> is selected from Group K, and  
 R<sub>2</sub> is selected from a side chain of an α-amino acid of Group A or is a member of Group J.
20. The process of claim 19 wherein the compound is selected from the group consisting of  
 30 Dns-Glu-Gly-Arg-C(O)C(O)NH<sub>2</sub> and  
 Dns-Glu-Gly-Phe(Gua)-C(O)C(O)NH<sub>2</sub>.
21. The process of claim 1 wherein  
 R is -OR<sup>1</sup> or -NR<sup>2</sup>R<sup>3</sup> wherein, R<sup>1</sup>, R<sup>2</sup>, and R<sup>3</sup> are each independently selected from hydrogen, a (C<sub>1</sub>-C<sub>6</sub>)alkyl group, (C<sub>2</sub>-C<sub>6</sub>)alkanoyl, phenyl, benzyl, benzoyl, cyclohexyl, cyclohexylmethyl or 2-pyridylmethyl,  
 35 R<sub>1</sub> is -P<sub>2</sub>-P<sub>3</sub>-P<sub>4</sub> with  
 P<sub>2</sub> being selected from Group E and K,  
 P<sub>3</sub> is selected from Group E or is deleted,  
 P<sub>4</sub> is selected from Group K or is deleted,  
 R<sub>2</sub> is selected from a side chain of an amino acid of Group A or is a member of Group J.
22. The process of claim 19 wherein the compound is selected from the group consisting of  
 40 Boc-Leu-Leu-Arg-C(O)C(O)NH<sub>2</sub>,  
 Boc-Leu-Leu-Phe(Gua)-C(O)C(O)OCH<sub>3</sub>, and  
 Bz-NHCH(J-1)-C(O)C(O)NH<sub>2</sub>.
23. The process of claim 1 wherein  
 45 R is -OR<sup>1</sup> or -NR<sup>2</sup>R<sup>3</sup> wherein, R<sup>1</sup>, R<sup>2</sup>, and R<sup>3</sup> are each independently selected from hydrogen, a (C<sub>1</sub>-C<sub>6</sub>)alkyl group, (C<sub>2</sub>-C<sub>6</sub>)alkanoyl, phenyl, benzyl, benzoyl, cyclohexyl, cyclohexylmethyl or 2-pyridylmethyl,  
 R<sub>1</sub> is P<sub>2</sub>,  
 P<sub>2</sub> being selected from Group K, and  
 R<sub>2</sub> is selected from a side chain of an amino acid of Groups E, G and C.
24. The process of claim 23 wherein the compound is  
 50  $\Phi$ CH<sub>2</sub>CONHCH<sub>2</sub>C(O)C(O)OCH<sub>3</sub>.
25. The process of claim 1 wherein  
 R is -OR<sup>1</sup> or -NR<sup>2</sup>R<sup>3</sup> wherein, R<sup>1</sup>, R<sup>2</sup>, and R<sup>3</sup> are each independently selected from hydrogen, a (C<sub>1</sub>-C<sub>6</sub>)alkyl group, (C<sub>2</sub>-C<sub>6</sub>)alkanoyl, phenyl, benzyl, benzoyl, cyclohexyl, cyclohexylmethyl or 2-pyridylmethyl  
 55 R<sub>1</sub> is P<sub>2</sub>-P<sub>3</sub> with  
 P<sub>2</sub> being Lys(Ac) or is selected from Groups E and C,  
 P<sub>3</sub> is selected from Group K, and  
 R<sub>2</sub> is a methyl group.

26. The process of claim 25 wherein the compound is Ac-Lys-(Ac)-ala-C(O)C(O)OH.
27. The process of claim 1 wherein R is -OR<sup>1</sup> or -NR<sup>2</sup>R<sup>3</sup> wherein, R<sup>1</sup>, R<sup>2</sup>, and R<sup>3</sup> are each independently selected from hydrogen, a (C<sub>1</sub>-C<sub>6</sub>)alkyl group, (C<sub>2</sub>-C<sub>6</sub>)alkanoyl, phenyl, benzyl, benzoyl, cyclohexyl, cyclohexylmethyl or 2-pyridylmethyl,
- 5 R<sub>1</sub> (a) -P<sub>2</sub>-P<sub>3</sub> or (b) -P<sub>2</sub>-P<sub>3</sub>-P<sub>4</sub> wherein (a) P<sub>2</sub> is selected from Groups E and F, and P<sub>3</sub> is selected from Group K, or (b) P<sub>2</sub> is selected from Groups E and F, P<sub>3</sub> being selected from Groups E and F, and
- 10 P<sub>4</sub> is selected from Group K, and R<sub>2</sub> is selected from the side chains of the α-amino acids of Group A or is a member of Group J or is ThrOCH<sub>2</sub>Φ.
28. The process of claim 27 wherein the compound is selected from the group consisting of
- 15 Cbz-Phe-NHCH(J-<sub>1</sub>)-C(O)C(O)OCH<sub>3</sub>, Ac-Leu-Leu-NHCH(J-<sub>1</sub>)-C(O)C(O)OH, and Ac-Leu-Leu-Arg-C(O)C(O)OH.
29. The process of Claim 1 wherein R is -OR<sup>1</sup> or -NR<sup>2</sup>R<sup>3</sup> wherein, R<sup>1</sup>, R<sup>2</sup>, and R<sup>3</sup> are each independently selected from hydrogen, a (C<sub>1</sub>-C<sub>6</sub>)alkyl group, (C<sub>2</sub>-C<sub>6</sub>)alkanoyl, phenyl, benzyl, benzoyl, cyclohexyl, cyclohexylmethyl, 2-pyridylmethyl or
- 20 isovaleryl amino (Iva), R<sub>1</sub> is -P<sub>2</sub>-P<sub>3</sub>-P<sub>4</sub>-P<sub>5</sub>-P<sub>6</sub> wherein P<sub>2</sub> is selected from Groups E, C, and F, P<sub>3</sub> is selected from Groups E and F or is deleted, P<sub>4</sub> is selected from Groups E, D, and F or is deleted,
- 25 P<sub>5</sub> is selected from Groups E, C, and F or is deleted, P<sub>6</sub> is selected from Group K or when P<sub>4</sub> is bVal or bAla, P<sub>5</sub> and P<sub>6</sub> are deleted, R<sub>2</sub> is selected from a side chain of an α-amino acid of Groups E or F or is cyclohexylmethylene.
30. The process of claim 29 wherein the compound is selected from the group consisting of
- 30 Cbz-Nal(1)-His-Leu-C(O)C(O)OCH<sub>2</sub>Φ, Cbz-Phe-His-Leu-C(O)C(O)NHCH<sub>2</sub>Φ, Boc-Phe-Nva-Leu-C(O)C(O)NHCH<sub>2</sub>Φ, Cbz-Phe-Nva-Leu-C(O)C(O)NHCH<sub>2</sub>Φ, Boc-His-Pro-Phe-His-Leu-C(O)C(O)NHCH<sub>2</sub>(2-pyridyl),
- 35 Cbz-Phe-His-Cha-C(O)C(O)OCH<sub>2</sub>Φ, Cbz-His-Leu-C(O)C(O)NHCH<sub>2</sub>Φ, Boc-Phe-His-Leu-C(O)C(O)OCH<sub>2</sub>Φ, Boc-Phe-Nva-Cha-C(O)C(O)NHCH<sub>2</sub>Φ, Boc-Tyr(Me)-Nva-Cha-C(O)C(O)Iva,
- 40 Boc-Phe-Ala(3pyr)-Cha-C(O)C(O)Iva, Tba-Tyr(Me)-Nva-Cha-C(O)C(O)Iva, Tba-Tyr(Me)-Ala(4pyr)-Cha-C(O)C(O)Iva, bAla-Tyr(Me)-Nva-Cha-C(O)C(O)Iva, bVal-Tyr(Me)-Nva-Cha-C(O)C(O)Iva,
- 45 bVal-Tyr(Me)-His-Cha-C(O)C(O)Iva, and bAla-Tyr(Me)-His-Cha-C(O)C(O)Iva.
31. The process of claim 1 wherein R is -OR<sup>1</sup> or -NR<sup>2</sup>R<sup>3</sup> wherein, R<sup>1</sup>, R<sup>2</sup>, and R<sup>3</sup> are each independently selected from hydrogen, a (C<sub>1</sub>-C<sub>6</sub>)alkyl group, (C<sub>2</sub>-C<sub>6</sub>)alkanoyl, phenyl, benzyl, benzoyl, cyclohexyl, cyclohexylmethyl, 2-pyridylmethyl or
- 50 isoamyl amino (Iaa) R<sub>1</sub> is -P<sub>2</sub>-P<sub>3</sub>-P<sub>4</sub> with P<sub>2</sub> being selected from Groups E and F, P<sub>3</sub> is selected from Groups E and F, P<sub>4</sub> is selected from Group K,
- 55 R<sub>2</sub> is selected from a side chain of an amino acid of Groups E and F.
32. The process of claim 31 wherein the compound is selected from the group consisting of Iva-Val-Leu-C(O)C(O)Iva and Iva-Val-Val-Leu-C(O)C(O)Iaa.

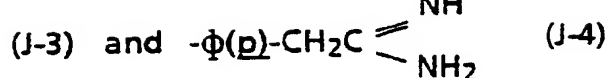
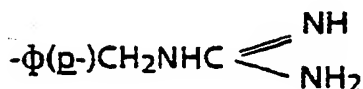
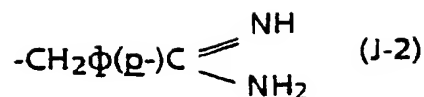
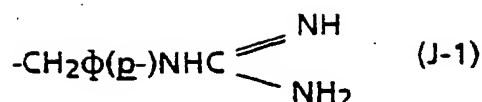
33. The process of claim 1 wherein  
 R is -OR<sup>1</sup> or -NR<sup>2</sup>R<sup>3</sup> wherein, R<sup>1</sup>, R<sup>2</sup>, and R<sup>3</sup> are each independently selected from hydrogen, a (C<sub>1</sub>-C<sub>6</sub>)alkyl group, (C<sub>2</sub>-C<sub>6</sub>)alkanoyl, phenyl, benzyl, benzoyl, cyclohexyl, cyclohexylmethyl or 2-pyridylmethyl,  
 R<sub>1</sub> is -P<sub>2</sub>-P<sub>3</sub>-P<sub>4</sub> with  
 5 P<sub>2</sub> being selected from Groups E and F,  
 P<sub>3</sub> is selected from Groups E and F or is deleted,  
 P<sub>4</sub> is selected from Group K,  
 R<sub>2</sub> is selected from a side chain of an amino acid of Groups E and F.
34. The process of claim 33 wherein the compound is selected from the group consisting of  
 10 CBz-Val-Val-Phe-C(O)C(O)Iva,  
 Iva-Val-Ala-Phe-C(O)C(O)CH<sub>2</sub>CH(CH<sub>3</sub>)<sub>2</sub>,  
 Iva-Val-Phe-C(O)C(O)Iva, and  
 Iva-Val-Phe-C(O)C(O)OCH<sub>3</sub>.
35. The process of claim 1 wherein  
 15 R is -OR<sup>1</sup> or -NR<sup>2</sup>R<sup>3</sup> wherein, R<sup>1</sup>, R<sup>2</sup>, and R<sup>3</sup> are each independently selected from hydrogen, a (C<sub>1</sub>-C<sub>6</sub>)alkyl group, (C<sub>2</sub>-C<sub>6</sub>)alkanoyl, phenyl, benzyl, benzoyl, cyclohexyl, cyclohexylmethyl or 2-pyridylmethyl,  
 R<sub>1</sub> is selected from Group K,  
 R<sub>2</sub> is selected from a side chain of an amino acid of Groups E, F and G.
36. The process of claim 35 wherein the compound is  
 20 Bz-Phe-C(O)C(O)OH.
37. The process of claim 1 wherein  
 R is -OR<sup>1</sup> or -NR<sup>2</sup>R<sup>3</sup> wherein, R<sup>1</sup>, R<sup>2</sup>, and R<sup>3</sup> are each independently selected from hydrogen, a (C<sub>1</sub>-C<sub>6</sub>)alkyl group, (C<sub>2</sub>-C<sub>6</sub>)alkanoyl, phenyl, benzyl, benzoyl, cyclohexyl, cyclohexylmethyl or 2-pyridylmethyl,  
 R<sub>1</sub> is -P<sub>2</sub>-P<sub>3</sub> with  
 25 P<sub>2</sub> being Gly and  
 P<sub>3</sub> being selected from Group F or is deleted, and  
 R<sub>2</sub> is H.
38. The process of claim 37 wherein the is  
 Tyr-Gly-Gly-C(O)C(O)OH.
39. The process of claim 1 wherein  
 30 R is -OR<sup>1</sup> or -NR<sup>2</sup>R<sup>3</sup> wherein, R<sup>1</sup>, R<sup>2</sup>, and R<sup>3</sup> are each independently selected from hydrogen, a (C<sub>1</sub>-C<sub>6</sub>)alkyl group, (C<sub>2</sub>-C<sub>6</sub>)alkanoyl, phenyl, benzyl, benzoyl, cyclohexyl, cyclohexylmethyl or 2-pyridylmethyl,  
 R<sub>1</sub> is -P<sub>2</sub>-P<sub>3</sub> with  
 P<sub>2</sub> being selected from Group E,  
 35 P<sub>3</sub> is selected from Group K, and  
 R<sub>2</sub> is selected from a side chain of an amino acid of Groups E and G.
40. The process of claim 39, wherein the compound is MeOSuc-Ala-Ala-C(O)C(O)NH<sub>2</sub>.
41. The process of claim 1 wherein  
 R is -OR<sup>1</sup> or -NR<sup>2</sup>R<sup>3</sup> wherein, R<sup>1</sup>, R<sup>2</sup>, and R<sup>3</sup> are each independently selected from hydrogen, a (C<sub>1</sub>-C<sub>6</sub>)alkyl group, (C<sub>2</sub>-C<sub>6</sub>)alkanoyl, phenyl, benzyl, benzoyl, cyclohexyl, cyclohexylmethyl or 2-pyridylmethyl,  
 40 R<sub>1</sub> is -P<sub>2</sub>-P<sub>3</sub> with  
 P<sub>2</sub> being selected from Groups E and F,  
 P<sub>3</sub> being selected from Groups C, E and F, the residues of which may be in either the D- or L-configuration,  
 and  
 45 R<sub>2</sub> is selected from a side chain of an amino acid of Group A or is a member of Group J.
42. The process of claim 41 wherein the compound is selected from the group consisting of  
 pro-Phe-Arg-C(O)C(O)OCH<sub>3</sub>,  
 pro-Phe-Arg-C(O)C(O)NH<sub>2</sub>, and  
 pro-Phe-NHCH(J-1)-C(O)C(O)OCH<sub>3</sub>.
43. The process of claim 1 wherein  
 50 R is -OR<sup>1</sup> or -NR<sup>2</sup>R<sup>3</sup> wherein, R<sup>1</sup>, R<sup>2</sup>, and R<sup>3</sup> are each independently selected from hydrogen, a (C<sub>1</sub>-C<sub>6</sub>)alkyl group, (C<sub>2</sub>-C<sub>6</sub>)alkanoyl, phenyl, benzyl, benzoyl, cyclohexyl, cyclohexylmethyl or 2-pyridylmethyl,  
 R<sub>1</sub> is -P<sub>2</sub>-P<sub>3</sub>-P<sub>4</sub> with  
 P<sub>2</sub> being selected from the Groups C, E, F and G,  
 55 P<sub>3</sub> being selected from the Groups C, E, F and G,  
 P<sub>4</sub> being selected from Group C, or being bAla or bVal, and optionally bearing an amino protecting group of Group K,  
 R<sub>2</sub> is a side chain of an amino acid of Groups F and E, or is a cyclohexylmethyl (CHM) group.

44. The process of claim 43 wherein the compound is selected from the group consisting of  
 Ser-Gln-Asn-Tyr-C(O)C(O)NH<sub>2</sub>,  
 Ser-Gln-Asn-Phe-C(O)C(O)NH(CHM),  
 Ser-Leu-Asn-Tyr-C(O)C(O)OH,  
 5 Ser-Leu-Asn-Phe-C(O)C(O)OH,  
 Thr-Gln-Asn-Tyr-C(O)C(O)NH(CHM),  
 Thr-Gln-Asn-Phe-C(O)C(O)NH(CHM),  
 Thr-Gln-Asn-Met-C(O)C(O)NH(CHM),  
 Iva-Ser-Asn-Tyr-C(O)C(O)Iva,  
 10 Iva-Ser-Asn-Phe-C(O)C(O)Iva,  
 Ser-Gln-Asn-Met-C(O)C(O)NH(CHM),  
 Ser-Leu-Asn-Met-C(O)C(O)NH(CHM),  
 Thr-Gln-Asn-Met-C(O)C(O)NH(CHM),  
 Thr-Leu-Asn-Met-C(O)C(O)NH(CHM),  
 15 Cbz-Phe-C(O)C(O)OCH<sub>2</sub>Φ,  
 Cbz-Phe-C(O)C(O)OCH<sub>2</sub>Φ,  
 Tba-Phe-Nva-Cha-C(O)C(O)Iva,  
 H-Phe-Nva-Cha-C(O)C(O)Iva,  
 Iva-Tyr(Me)-Nva-Cha-C(O)C(O)Iva),  
 20 BOC-Phe-C(O)C(O)NH<sub>2</sub>,  
 Cbz-Phe-C(O)C(O)N(CH<sub>3</sub>)CH<sub>2</sub>C<sub>6</sub>H<sub>5</sub>, and  
 Cbz-Phe-C(O)C(O)OEt.  
 45. The process of claim 1 wherein  
 R is -OR<sup>1</sup> or -NR<sup>2</sup>R<sup>3</sup> wherein, R<sup>1</sup>, R<sup>2</sup>, and R<sup>3</sup> are each independently selected from hydrogen, a (C<sub>1</sub>-C<sub>6</sub>)alkyl  
 25 group, (C<sub>2</sub>-C<sub>6</sub>)alkanoyl, phenyl, benzyl, benzoyl, cyclohexyl, cyclohexylmethyl or 2-pyridylmethyl,  
 R<sub>1</sub> is -P<sub>2</sub>-P<sub>3</sub> wherein  
 P<sub>2</sub> is selected from Group E,  
 P<sub>3</sub> is selected from Group K, and  
 R<sub>2</sub> is selected from a side chain of an amino acid from Group E.

30 Claims for the following Contracting State: GR

1. A compound of the formula I:  
**R<sub>1</sub>NHCH(R<sub>2</sub>)C(O)C(O)C(O)R** (I)  
 35 the hydrates, isosteres or the pharmaceutically acceptable salts thereof wherein  
 R is -OR<sup>1</sup> or -NR<sup>2</sup>R<sup>3</sup> wherein, R<sup>1</sup>, R<sup>2</sup>, and R<sup>3</sup> are each independently selected from hydrogen, a (C<sub>1</sub>-C<sub>6</sub>)alkyl  
 group, (C<sub>2</sub>-C<sub>6</sub>)alkanoyl, phenyl, benzyl, benzoyl, cyclohexyl, cyclohexylmethyl or 2-pyridylmethyl,  
 R<sub>1</sub> is an amino protecting group selected from Group K, an α-amino acid or a peptide comprised of a  
 number of α-amino acid building blocks, each of said α-amino acid or peptide optionally bearing an amino  
 40 protecting group preferably selected from Group K,  
 R<sub>2</sub> is a side chain of an α-amino acid responsible for directing the inhibitor to the active site of the enzyme  
 wherein the said α-amino acid and peptide moieties are building blocks selected from Groups A, B, C, D, E,  
 F, and G or wherein R<sub>2</sub> is a member of the Group J, and K is a terminal amino protecting group, members  
 of these groups being  
 45 Group A: Lys and Arg  
 B: Glu, Asp  
 C: Ser, Thr, Gln, Asn, Cys, His, Ala (3pyr), Ala (4pyr) and N-methyl derivatives  
 D: Pro, Ind  
 E: Ala, Leu, Ile, Val, Nva, Met, bVal, bAla, Nle and N-methyl derivatives  
 50 F: Phe, Tyr, Tyr(Me) Ala(3pyr) Ala(4pyr) Trp, Nal(1), and N-methyl derivatives  
 G: Gly, Sar  
 J:

55

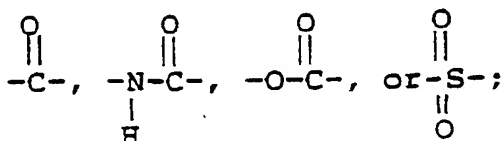


with  $\Phi$  representing phenyl,

K: Acetyl (Ac), Succinyl (Suc), Benzoyl (Bz), t-Butyloxycarbonyl (Boc), Carbobenzyloxy (Cbz), Tosyl (Ts), Dansyl (Dns), Isovaleryl (Iva), Methoxysuccinyl (MeOSuc), 1-Adamantanesulfonyl (AdSO<sub>2</sub>), 1-Adamantaneacetyl (AdAc), 2-Carboxybenzoyl (2CBz), Phenylacetyl (PhAc), t-Butylacetyl (Tba), bis [(1-naphthyl)-methyl]acetyl (BNMA),

or -A-R<sub>2</sub> wherein

A is



and

R<sub>2</sub> is an aryl group containing 6, 10 or 12 carbons suitably substituted by 1 to 3 members selected independently from the group consisting of fluoro, chloro, bromo, iodo, trifluoromethyl, hydroxy, alkyl containing from 1 to 6 carbons, alkoxy containing from 1 to 6 carbons, carboxy, alkylcarbonylamino wherein the alkyl group contains 1 to 6 carbons, 5-tetrazoly, and acylsulfonamido (i.e., acylaminosulfonyl and sulfonylamino carbonyl "Sac") containing from 1 to 15 carbons, provided that when the acylsulfonamido contains an aryl the aryl may be further substituted by a member selected from fluoro, chloro, bromo, iodo and nitro; and such other terminal amino protecting groups which are functionally equivalent thereto.

2. A compound of claim 1 wherein

R is -OR<sup>1</sup> or -NR<sup>2</sup>R<sup>3</sup> wherein, R<sup>1</sup>, R<sup>2</sup>, and R<sup>3</sup> are each independently selected from hydrogen, a (C<sub>1</sub>-C<sub>6</sub>)alkyl group, (C<sub>2</sub>-C<sub>6</sub>)alkanoyl, phenyl, benzyl, benzoyl, cyclohexyl, cyclohexylmethyl or 2-pyridylmethyl,

R<sub>1</sub> is -P<sub>2</sub>-P<sub>3</sub>-P<sub>4</sub>-P<sub>5</sub> with

P<sub>2</sub> being an α-amino acid selected from Groups D, E and F,

P<sub>3</sub> is an α-amino acid of Group D and E, or is lysine,

P<sub>4</sub> is an α-amino acid of Group E or is deleted,

P<sub>5</sub> is a member of Group K,

R<sub>2</sub> is a side chain of an amino acid of Groups E or G.

3. A compound of claim 1 selected from the group consisting of

MeOSuc-Ala-Ala-Pro-Val-C(O)C(O)NH<sub>2</sub>,

AdSO<sub>2</sub>-Lys(2CBz)-Pro-Val-C(O)C(O)NH<sub>2</sub>,

Cbz-Val-Pro-Val-C(O)C(O)NH<sub>2</sub>,

ClΦSacBz-Val-Pro-Val-C(O)C(O)NH<sub>2</sub>,

BrΦSacBz-Val-Pro-Val-C(O)C(O)NH<sub>2</sub>,

ΦSacBz-Val-Pro-Val-C(O)C(O)NH<sub>2</sub>, and

tPht-Val-Pro-Val-C(O)C(O)NH<sub>2</sub>.

4. A compound of claim 1 wherein

R is -OR<sup>1</sup> or -NR<sup>2</sup>R<sup>3</sup> wherein, R<sup>1</sup>, R<sup>2</sup>, and R<sup>3</sup> are each independently selected from hydrogen, a (C<sub>1</sub>-C<sub>6</sub>)alkyl group, (C<sub>2</sub>-C<sub>6</sub>)alkanoyl, phenyl, benzyl, benzoyl, cyclohexyl, cyclohexylmethyl or 2-pyridylmethyl,

R<sub>1</sub> is -P<sub>2</sub>-P<sub>3</sub>-P<sub>4</sub>-P<sub>5</sub> with

P<sub>2</sub> being selected from Groups D, E, and G,

- $P_3$  is selected from Groups E and G,  
 $P_4$  is selected from Groups E and G or is deleted,  
 $P_5$  is a member of Group K,  
 $R_2$  is selected from a side chain of an amino acid of Groups E and F.
5. A compound of claim 4 selected from the group consisting of  
 MeOSuc-Ala-Ala-Pro-Phe-C(O)C(O)OH,  
 Suc-Ala-Ala-Pro-Phe-C(O)C(O)OH, and  
 Cl $\Phi$ SacBz-Val-Pro-Phe-C(O)C(O)OH.
6. A compound of claim 1 wherein  
 10  $R$  is  $-OR^1$  or  $-NR^2R^3$  wherein,  $R^1$ ,  $R^2$ , and  $R^3$  are each independently selected from hydrogen, a  $(C_1-C_6)$ alkyl group,  $(C_2-C_6)$ alkanoyl, phenyl, benzyl, benzoyl, cyclohexyl, cyclohexylmethyl or 2-pyridylmethyl,  
 $R_1$  is (a)- $P_2$ - $P_3$ , (b)  $-P_2$  or (c)  $-P_2$ - $P_3$ - $P_4$  wherein  
 (a)  $P_2$  is selected from Groups D, E and F,  
 $P_3$  is selected from Group F, each  $P_3$  being in the D-configuration,
- 15 (b)  $P_2$  is selected from Group K,  
 (c)  $P_2$  is selected from Group E,  
 $P_3$  is selected from Groups C, G and E,  
 $P_4$  is selected from Groups F, G and E or is deleted,  
 $R_2$  is the arginine side chain, or is selected from a side chain of an amino acid of Group A or is a member
- 20 of Group J.
7. A compound of claim 6 selected from the group consisting of  
 phe-Pro-NHCH(J-I)-C(O)C(O)OH,  
 phe-Pro-Arg-C(O)C(O)OH,  
 Dns-Arg-C(O)C(O)OH,  
 25 Phe-Ser-Ala-C(O)C(O)OH,  
 phe-Pro-Lys-C(O)C(O)OH, and  
 Bz-NHCH(J-I)-C(O)C(O)OH.
8. A compound of claim 1 wherein  
 $R$  is  $-OR^1$  or  $-NR^2R^3$  wherein,  $R^1$ ,  $R^2$ , and  $R^3$  are each independently selected from hydrogen, a  $(C_1-C_6)$ alkyl
- 30 group,  $(C_2-C_6)$ alkanoyl, phenyl, benzyl, benzoyl, cyclohexyl, cyclohexylmethyl or 2-pyridylmethyl,  
 $R_1$  is  $-P_2$ - $P_3$ - $P_4$ - $P_5$  with  
 $P_2$  being selected from Groups D, E, G and K,  
 $P_3$  is selected from Groups E, G and K or is deleted,  
 $P_4$  is selected from Groups E, G and K or is deleted,
- 35  $P_5$  is selected from Group K or is deleted, and  
 $R_2$  is selected from a side chain of an amino acid of Groups E and F.
9. A compound of claim 1 selected from the group consisting of  
 Bz-Phe-C(O)C(O)OCH<sub>3</sub>,  
 Bz-Tyr-C(O)C(O)OCH<sub>3</sub> and  
 40 Ac-Leu-Phe-C(O)C(O)OCH<sub>3</sub>.
10. A compound of claim 1 wherein  
 $R_2$  is the arginine side chain, or is selected from a side chain of an amino acid of Groups A and J,  
 $R_1$  is selected from (a)- $P_2$ - $P_3$ , (b)- $P_2$  or (c)- $P_2$ - $P_3$ - $P_4$  with  
 (a)  $P_2$  is selected from Groups D, E or F,  $P_3$  is selected from Group F, (each being in the D-
- 45 configuration),  
 (b)  $P_2$  is selected from Group K,  
 (c)  $P_2$  is selected from Group D or E,  $P_3$  is selected from Groups G and E,  $P_4$  is selected from Groups G and E or is deleted.
11. A compound of claim 1 wherein  
 50  $R$  is  $-OR^1$  or  $-NR^2R^3$  wherein,  $R^1$ ,  $R^2$ , and  $R^3$  are each independently selected from hydrogen, a  $(C_1-C_6)$ alkyl group,  $(C_2-C_6)$ alkanoyl, phenyl, benzyl, benzoyl, cyclohexyl, cyclohexylmethyl or 2-pyridylmethyl,  
 $R_1$  is  $-P_2$ - $P_3$ - $P_4$  with  
 $P_2$  being selected from Group E and F,  
 $P_3$  is selected from Groups B, F and K, and
- 55  $P_4$  is selected from Group K,  
 $R_2$  is selected from a side chain of an amino acid of Group A or is a member of Group J.
12. A compound of claim 11 selected from the group consisting of  
 Dns-Glu-Phe-Lys-C(O)C(O)OCH<sub>3</sub>,

Ac-Ala-NHCH(J-1)-C(O)C(O)OCH<sub>3</sub>, and  
Ac-Ala-Lys-C(O)C(O)OCH<sub>3</sub>.

13. A compound of claim 1 wherein

R is -OR<sup>1</sup> or -NR<sup>2</sup>R<sup>3</sup> wherein, R<sup>1</sup>, R<sup>2</sup>, and R<sup>3</sup> are each independently selected from hydrogen, a (C<sub>1</sub>-C<sub>6</sub>)alkyl group, (C<sub>2</sub>-C<sub>6</sub>)alkanoyl, phenyl, benzyl, benzoyl, cyclohexyl, cyclohexylmethyl

R<sub>1</sub> is -P<sub>2</sub>-P<sub>3</sub> with

P<sub>2</sub> being selected from Groups E, G, D, C, F, A and B,

P<sub>3</sub> is selected from Group K,

R<sub>2</sub> is selected from a side chain of an amino acid of Group A or is a member of Group J.

14. A compound of claim 13 selected from the group consisting of

Cbz-Ala-Arg-C(O)C(O)NH<sub>2</sub>,

Ac-Ala-NHCH(J-1)-C(O)C(O)OCH<sub>3</sub>.

15. A compound of claim 1 wherein

R is -OR<sup>1</sup> or -NR<sup>2</sup>R<sup>3</sup> wherein, R<sup>1</sup>, R<sup>2</sup>, and R<sup>3</sup> are each independently selected from hydrogen, a (C<sub>1</sub>-C<sub>6</sub>)alkyl group, (C<sub>2</sub>-C<sub>6</sub>)alkanoyl, phenyl, benzyl, benzoyl, cyclohexyl, cyclohexylmethyl or 2-pyridylmethyl,

R<sub>1</sub> is -P<sub>2</sub>-P<sub>3</sub>-P<sub>4</sub> with

P<sub>2</sub> being selected from Groups E and F,

P<sub>3</sub> is selected from Groups E and F, and

P<sub>4</sub> is selected from Group K,

R<sub>2</sub> is selected from a side chain of an amino acid of Group A or is a member of Group J.

16. A compound of claim 15 which is

Bz-Leu-Ala-Arg-C(O)C(O)NH<sub>2</sub>.

17. A compound of claim 1 wherein

R is -OR<sup>1</sup> or -NR<sup>2</sup>R<sup>3</sup> wherein, R<sup>1</sup>, R<sup>2</sup>, and R<sup>3</sup> are each independently selected from hydrogen, a (C<sub>1</sub>-C<sub>6</sub>)alkyl group, (C<sub>2</sub>-C<sub>6</sub>)alkanoyl, phenyl, benzyl, benzoyl, cyclohexyl, cyclohexylmethyl or 2-pyridylmethyl,

R<sub>1</sub> is -P<sub>2</sub>-P<sub>3</sub> with

P<sub>2</sub> being selected from Groups E and G,

P<sub>3</sub> is selected from Group B, and

R<sub>2</sub> is selected from a side chain of an amino acid of Group A or is a member of Group J.

18. A compound of claim 17 selected from the group consisting of

K-Glu-Gly-Arg-C(O)C(O)NH<sub>2</sub> and

K-Glu-Gly-Phe(Gua)-C(O)C(O)NH<sub>2</sub>.

19. A compound of claim 1 wherein

R is -OR<sup>1</sup> or -NR<sup>2</sup>R<sup>3</sup> wherein, R<sup>1</sup>, R<sup>2</sup>, and R<sup>3</sup> are each independently selected from hydrogen, a (C<sub>1</sub>-C<sub>6</sub>)alkyl group, (C<sub>2</sub>-C<sub>6</sub>)alkanoyl, phenyl, benzyl, benzoyl, cyclohexyl, cyclohexylmethyl or 2-pyridylmethyl,

R<sub>1</sub> is -P<sub>2</sub>-P<sub>3</sub>-P<sub>4</sub> with

P<sub>2</sub> is Gly,

P<sub>3</sub> is selected from Group B, and

P<sub>4</sub> is selected from Group K, and

R<sub>2</sub> is selected from a side chain of an α-amino acid of Group A or is a member of Group J.

20. A compound of claim 19 selected from the group consisting of

Dns-Glu-Gly-Arg-C(O)C(O)NH<sub>2</sub> and

Dns-Glu-Gly-Phe(Gua)-C(O)C(O)NH<sub>2</sub>.

21. A compound of claim 1 wherein

R is -OR<sup>1</sup> or -NR<sup>2</sup>R<sup>3</sup> wherein, R<sup>1</sup>, R<sup>2</sup>, and R<sup>3</sup> are each independently selected from hydrogen, a (C<sub>1</sub>-C<sub>6</sub>)alkyl group, (C<sub>2</sub>-C<sub>6</sub>)alkanoyl, phenyl, benzyl, benzoyl, cyclohexyl, cyclohexylmethyl or 2-pyridylmethyl,

R<sub>1</sub> is -P<sub>2</sub>-P<sub>3</sub>-P<sub>4</sub> with

P<sub>2</sub> being selected from Group E and K,

P<sub>3</sub> is selected from Group E or is deleted,

P<sub>4</sub> is selected from Group K or is deleted,

R<sub>2</sub> is selected from a side chain of an amino acid of Group A or is a member of Group J.

22. A compound of claim 19 selected from the group consisting of

Boc-Leu-Leu-Arg-C(O)C(O)NH<sub>2</sub>,

Boc-Leu-Leu-Phe(Gua)-C(O)C(O)OCH<sub>3</sub>, and

Bz-NHCH(J-1)-C(O)C(O)NH<sub>2</sub>.

23. A compound of claim 1 wherein

R is -OR<sup>1</sup> or -NR<sup>2</sup>R<sup>3</sup> wherein, R<sup>1</sup>, R<sup>2</sup>, and R<sup>3</sup> are each independently selected from hydrogen, a (C<sub>1</sub>-C<sub>6</sub>)alkyl group, (C<sub>2</sub>-C<sub>6</sub>)alkanoyl, phenyl, benzyl, benzoyl, cyclohexyl, cyclohexylmethyl or 2-pyridylmethyl,



- R<sub>1</sub> is P<sub>2</sub>,  
P<sub>2</sub> being selected from Group K, and  
R<sub>2</sub> is selected from a side chain of an amino acid of Groups E, G and C.
24. A compound of claim 23 consisting of
- 5  $\Phi\text{CH}_2\text{CONHCH}_2\text{C}(\text{O})\text{C}(\text{O})\text{OCH}_3$ .
25. A compound of claim 1 wherein  
R is -OR<sup>1</sup> or -NR<sup>2</sup>R<sup>3</sup> wherein, R<sup>1</sup>, R<sup>2</sup>, and R<sup>3</sup> are each independently selected from hydrogen, a (C<sub>1</sub>-C<sub>6</sub>)alkyl group, (C<sub>2</sub>-C<sub>6</sub>)alkanoyl, phenyl, benzyl, benzoyl, cyclohexyl, cyclohexylmethyl or 2-pyridylmethyl  
R<sub>1</sub> is P<sub>2</sub>-P<sub>3</sub> with
- 10 P<sub>2</sub> being Lys(Ac) or is selected from Groups E and C,  
P<sub>3</sub> is selected from Group K, and  
R<sub>2</sub> is a methyl group.
26. A compound of claim 25 which is  
Ac-Lys-(Ac)-ala-C(O)C(O)OH.
- 15 27. A compound of claim 1 wherein  
R is -OR<sup>1</sup> or -NR<sup>2</sup>R<sup>3</sup> wherein, R<sup>1</sup>, R<sup>2</sup>, and R<sup>3</sup> are each independently selected from hydrogen, a (C<sub>1</sub>-C<sub>6</sub>)alkyl group, (C<sub>2</sub>-C<sub>6</sub>)alkanoyl, phenyl, benzyl, benzoyl, cyclohexyl, cyclohexylmethyl or 2-pyridylmethyl,  
R<sub>1</sub> (a) -P<sub>2</sub>-P<sub>3</sub> or (b) -P<sub>2</sub>-P<sub>3</sub>-P<sub>4</sub> wherein  
(a) P<sub>2</sub> is selected from Groups E and F, and
- 20 P<sub>3</sub> is selected from Group K, or  
(b) P<sub>2</sub> is selected from Groups E and F,  
P<sub>3</sub> being selected from Groups E and F, and  
P<sub>4</sub> is selected from Group K, and  
R<sub>2</sub> is selected from the side chains of the  $\alpha$ -amino acids of Group A or is a member of Group J or is
- 25 ThrOCH<sub>2</sub> $\Phi$ .
28. A compound of claim 27 selected from the group consisting of  
Cbz-Phe-NHCH(J-1)-C(O)C(O)OCH<sub>3</sub>,  
Ac-Leu-Leu-NHCH(J-1)-C(O)C(O)OH, and  
Ac-Leu-Leu-Arg-C(O)C(O)OH.
- 30 29. A compound of Claim 1 wherein  
R is -OR<sup>1</sup> or -NR<sup>2</sup>R<sup>3</sup> wherein, R<sup>1</sup>, R<sup>2</sup>, and R<sup>3</sup> are each independently selected from hydrogen, a (C<sub>1</sub>-C<sub>6</sub>)alkyl group, (C<sub>2</sub>-C<sub>6</sub>)alkanoyl, phenyl, benzyl, benzoyl, cyclohexyl, cyclohexylmethyl, 2-pyridylmethyl or isovaleryl amino (Iva),  
R<sub>1</sub> is -P<sub>2</sub>-P<sub>3</sub>-P<sub>4</sub>-P<sub>5</sub>-P<sub>6</sub> wherein
- 35 P<sub>2</sub> is selected from Groups E, C, and F,  
P<sub>3</sub> is selected from Groups E and F or is deleted,  
P<sub>4</sub> is selected from Groups E, D, and F or is deleted,  
P<sub>5</sub> is selected from Groups E, C, and F or is deleted,  
P<sub>6</sub> is selected from Group K or when P<sub>4</sub> is bVal or bAla, P<sub>5</sub> and P<sub>6</sub> are deleted,
- 40 R<sub>2</sub> is selected from a side chain of an  $\alpha$ -amino acid of Groups E or F or is cyclohexylmethylene.
30. A compound of claim 29 selected from the group consisting of  
Cbz-Nal(1)-His-Leu-C(O)C(O)OCH<sub>2</sub> $\Phi$ ,  
Cbz-Phe-His-Leu-C(O)C(O)NHCH<sub>2</sub> $\Phi$ ,  
Boc-Phe-Nva-Leu-C(O)C(O)NHCH<sub>2</sub> $\Phi$ ,  
45 Cbz-Phe-Nva-Leu-C(O)C(O)NHCH<sub>2</sub> $\Phi$ ,  
Boc-His-Pro-Phe-His-Leu-C(O)C(O)NHCH<sub>2</sub>(2-pyridyl),  
Cbz-Phe-His-Cha-C(O)C(O)OCH<sub>2</sub> $\Phi$ ,  
Cbz-His-Leu-C(O)C(O)NHCH<sub>2</sub> $\Phi$ ,  
Boc-Phe-His-Leu-C(O)C(O)OCH<sub>2</sub> $\Phi$ ,  
50 Boc-Phe-Nva-Cha-C(O)C(O)NHCH<sub>2</sub> $\Phi$ ,  
Boc-Tyr(Me)-Nva-Cha-C(O)C(O)Iva,  
Boc-Phe-Ala(3pyr)-Cha-C(O)C(O)Iva,  
Tba-Tyr(Me)-Nva-Cha-C(O)C(O)Iva,  
Tba-Tyr(Me)-Ala(4pyr)-Cha-C(O)C(O)Iva,  
55 bAla-Tyr(Me)-Nva-Cha-C(O)C(O)Iva,  
bVal-Tyr(Me)-Nva-Cha-C(O)C(O)Iva,  
bVal-Tyr(Me)-His-Cha-C(O)C(O)Iva, and  
bAla-Tyr(Me)-His-Cha-C(O)C(O)Iva.

31. A compound of claim 1 wherein  
 R is -OR<sup>1</sup> or -NR<sup>2</sup>R<sup>3</sup> wherein, R<sup>1</sup>, R<sup>2</sup>, and R<sup>3</sup> are each independently selected from hydrogen, a (C<sub>1</sub>-C<sub>6</sub>)alkyl group, (C<sub>2</sub>-C<sub>6</sub>)alkanoyl, phenyl, benzyl, benzoyl, cyclohexyl, cyclohexylmethyl, 2-pyridylmethyl or isoamylamino (Iaa)
- 5 R<sub>1</sub> is -P<sub>2</sub>-P<sub>3</sub>-P<sub>4</sub> with  
 P<sub>2</sub> being selected from Groups E and F,  
 P<sub>3</sub> is selected from Groups E and F,  
 P<sub>4</sub> is selected from Group K,  
 R<sub>2</sub> is selected from a side chain of an amino acid of Groups E and F.
- 10 32. A compound of claim 31 selected from the group consisting of  
 Iva-Val-Leu-C(O)C(O)Iva and  
 Iva-Val-Val-Leu-C(O)C(O)Iaa.
33. A compound of claim 1 wherein  
 R is -OR<sup>1</sup> or -NR<sup>2</sup>R<sup>3</sup> wherein, R<sup>1</sup>, R<sup>2</sup>, and R<sup>3</sup> are each independently selected from hydrogen, a (C<sub>1</sub>-C<sub>6</sub>)alkyl group, (C<sub>2</sub>-C<sub>6</sub>)alkanoyl, phenyl, benzyl, benzoyl, cyclohexyl, cyclohexylmethyl or 2-pyridylmethyl,
- 15 R<sub>1</sub> is P<sub>2</sub>-P<sub>3</sub>-P<sub>4</sub> with  
 P<sub>2</sub> being selected from Groups E and F,  
 P<sub>3</sub> is selected from Groups E and F or is deleted,  
 P<sub>4</sub> is selected from Group K,  
 R<sub>2</sub> is selected from a side chain of an amino acid of Groups E and F.
- 20 34. A compound of claim 33 selected from the group consisting of  
 CBz-Val-Val-Phe-C(O)C(O)Iva,  
 Iva-Val-Ala-Phe-C(O)C(O)CH<sub>2</sub>CH(CH<sub>3</sub>)<sub>2</sub>,  
 Iva-Val-Phe-C(O)C(O)Iva, and  
 Iva-Val-Phe-C(O)C(O)OCH<sub>3</sub>.
- 25 35. A compound of claim 1 wherein  
 R is -OR<sup>1</sup> or -NR<sup>2</sup>R<sup>3</sup> wherein, R<sup>1</sup>, R<sup>2</sup>, and R<sup>3</sup> are each independently selected from hydrogen, a (C<sub>1</sub>-C<sub>6</sub>)alkyl group, (C<sub>2</sub>-C<sub>6</sub>)alkanoyl, phenyl, benzyl, benzoyl, cyclohexyl, cyclohexylmethyl or 2-pyridylmethyl,  
 R<sub>1</sub> is selected from Group K,  
 R<sub>2</sub> is selected from a side chain of an amino acid of Groups E, F and G.
- 30 36. A compound of claim 35 consisting of  
 Bz-Phe-C(O)C(O)OH.
37. A compound of claim 1 wherein  
 R is -OR<sup>1</sup> or -NR<sup>2</sup>R<sup>3</sup> wherein, R<sup>1</sup>, R<sup>2</sup>, and R<sup>3</sup> are each independently selected from hydrogen, a (C<sub>1</sub>-C<sub>6</sub>)alkyl group, (C<sub>2</sub>-C<sub>6</sub>)alkanoyl, phenyl, benzyl, benzoyl, cyclohexyl, cyclohexylmethyl or 2-pyridylmethyl,
- 35 R<sub>1</sub> is -P<sub>2</sub>-P<sub>3</sub> with  
 P<sub>2</sub> being Gly and  
 P<sub>3</sub> being selected from Group F or is deleted, and R<sub>2</sub> is H.
38. A compound of claim 37 which is  
 Tyr-Gly-Gly-C(O)C(O)OH.
- 40 39. A compound of claim 1 wherein  
 R is -OR<sup>1</sup> or -NR<sup>2</sup>R<sup>3</sup> wherein, R<sup>1</sup>, R<sup>2</sup>, and R<sup>3</sup> are each independently selected from hydrogen, a (C<sub>1</sub>-C<sub>6</sub>)alkyl group, (C<sub>2</sub>-C<sub>6</sub>)alkanoyl, phenyl, benzyl, benzoyl, cyclohexyl, cyclohexylmethyl or 2-pyridylmethyl,  
 R<sub>1</sub> is -P<sub>2</sub>-P<sub>3</sub> with
- 45 P<sub>2</sub> being selected from Group E,  
 P<sub>3</sub> is selected from Group K, and  
 R<sub>2</sub> is selected from a side chain of an amino acid of Groups E and G.
40. A compound of claim 39, said compound being MeOSuc-Ala-Ala-C(O)C(O)NH<sub>2</sub>.
41. A compound of claim 1 wherein
- 50 R is -OR<sup>1</sup> or -NR<sup>2</sup>R<sup>3</sup> wherein, R<sup>1</sup>, R<sup>2</sup>, and R<sup>3</sup> are each independently selected from hydrogen, a (C<sub>1</sub>-C<sub>6</sub>)alkyl group, (C<sub>2</sub>-C<sub>6</sub>)alkanoyl, phenyl, benzyl, benzoyl, cyclohexyl, cyclohexylmethyl or 2-pyridylmethyl,  
 R<sub>1</sub> is -P<sub>2</sub>-P<sub>3</sub> with  
 P<sub>2</sub> being selected from Groups E and F,  
 P<sub>3</sub> being selected from Groups C, E and F, the residues of which may be in either the D- or L-configuration,
- 55 and  
 R<sub>2</sub> is selected from a side chain of an amino acid of Group A or is a member of Group J.
42. A compound of claim 41 selected from the group consisting of  
 pro-Phe-Arg-C(O)C(O)OCH<sub>3</sub>,

pro-Phe-Arg-C(O)C(O)NH<sub>2</sub>, and  
 pro-Phe-NHCH(J-1)-C(O)C(O)OCH<sub>3</sub>.

43. A compound of claim 1 wherein

R is -OR<sup>1</sup> or -NR<sup>2</sup>R<sup>3</sup> wherein, R<sup>1</sup>, R<sup>2</sup>, and R<sup>3</sup> are each independently selected from hydrogen, a (C<sub>1</sub>-C<sub>6</sub>)alkyl group, (C<sub>2</sub>-C<sub>6</sub>)alkanoyl, phenyl, benzyl, benzoyl, cyclohexyl, cyclohexylmethyl or 2-pyridylmethyl,

R<sub>1</sub> is -P<sub>2</sub>-P<sub>3</sub>-P<sub>4</sub> with

P<sub>2</sub> being selected from the Groups C, E, F and G,

P<sub>3</sub> being selected from the Groups C, E, F and G,

P<sub>4</sub> being selected from Group C, or being bAla or bVal, and optionally bearing an amino protecting group of Group K,

R<sub>2</sub> is a side chain of an amino acid of Groups F and E, or is a cyclohexylmethyl (CHM) group.

44. A compound of claim 43 selected from the group consisting of

Ser-Gln-Asn-Tyr-C(O)C(O)NH<sub>2</sub>,

Ser-Gln-Asn-Phe-C(O)C(O)NH(CHM),

15 Ser-Leu-Asn-Tyr-C(O)C(O)OH,

Ser-Leu-Asn-Phe-C(O)C(O)OH,

Thr-Gln-Asn-Tyr-C(O)C(O)NH(CHM),

Thr-Gln-Asn-Phe-C(O)C(O)NH(CHM),

Thr-Gln-Asn-Met-C(O)C(O)NH(CHM),

20 Iva-Ser-Asn-Tyr-C(O)C(O)Iva,

Iva-Ser-Asn-Phe-C(O)C(O)Iva,

Ser-Gln-Asn-Met-C(O)C(O)NH(CHM),

Ser-Leu-Asn-Met-C(O)C(O)NH(CHM),

Thr-Gln-Asn-Met-C(O)C(O)NH(CHM),

25 Thr-Leu-Asn-Met-C(O)C(O)NH(CHM),

Cbz-Phe-C(O)C(O)OCH<sub>2</sub>Φ,

Cbz-Phe-C(O)C(O)OCH<sub>2</sub>Φ,

Tba-Phe-Nva-Cha-C(O)C(O)Iva,

H-Phe-Nva-Cha-C(O)C(O)Iva,

30 Iva-Tyr(Me)-Nva-Cha-C(O)C(O)Iva),

BOC-Phe-C(O)C(O)NH<sub>2</sub>,

Cbz-Phe-C(O)C(O)N(CH<sub>3</sub>)CH<sub>2</sub>C<sub>6</sub>H<sub>5</sub>, and

Cbz-Phe-C(O)C(O)OEt.

45. A compound of claim 1 wherein

35 R is -OR<sup>1</sup> or -NR<sup>2</sup>R<sup>3</sup> wherein, R<sup>1</sup>, R<sup>2</sup>, and R<sup>3</sup> are each independently selected from hydrogen, a (C<sub>1</sub>-C<sub>6</sub>)alkyl group, (C<sub>2</sub>-C<sub>6</sub>)alkanoyl, phenyl, benzyl, benzoyl, cyclohexyl, cyclohexylmethyl or 2-pyridylmethyl,

R<sub>1</sub> is -P<sub>2</sub>-P<sub>3</sub> wherein

P<sub>2</sub> is selected from Group E

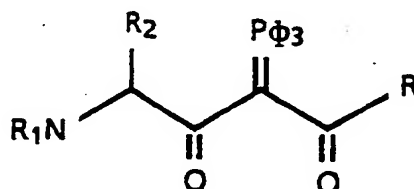
P<sub>3</sub> is selected from Group K, and

40 R<sub>2</sub> is selected from a side chain of an amino acid from Group E.

46. A process for preparing a compound of the formula

**R<sub>1</sub>NHCH(R<sub>2</sub>)C(O)C(O)C(O)R**

wherein R, R<sub>1</sub> and R<sub>2</sub> are as defined in Claim 1 which comprises treating a solution of a compound of the formula



with either a) singlet oxygen or b) excess ozone followed by dimethylsulfide, and isolating the product.

55 47. The compounds of claim 1 for use as a pharmaceutically active substance.

48. The use of the compounds of claim 1 for the preparation of a pharmaceutical composition to inhibit peptidases and isomerases.

SEQUENCE LISTING

SEQ ID NO: 1  
SEQUENCE TYPE: Amino Acid  
SEQUENCE LENGTH: 4 amino acids  
TOPOLOGY: linear  
TYPE OF MOLECULE SEQUENCED: peptide or protein  
SEQUENCE DESCRIPTION:

Ala-Ala-Pro-Val

OTHER INFORMATION: N-terminal nitrogen is methoxysuccinyl substituted; C-terminal carboxy group is replaced with a carboxyoxalyl group.

SEQ ID NO: 2  
SEQUENCE TYPE: Amino Acid  
SEQUENCE LENGTH: 4 amino acids  
TOPOLOGY: linear  
TYPE OF MOLECULE SEQUENCED: peptide or protein  
SEQUENCE DESCRIPTION:

Ala-Ala-Pro-Phe

OTHER INFORMATION: N-terminal nitrogen is methoxysuccinyl substituted; C-terminal carboxy group is replaced with a carboxyoxalyl group.

SEQ ID NO: 3  
SEQUENCE TYPE: Amino Acid  
SEQUENCE LENGTH: 4 amino acids  
TOPOLOGY: linear  
TYPE OF MOLECULE SEQUENCED: peptide or protein  
SEQUENCE DESCRIPTION:

Ala-Ala-Pro-Phe

OTHER INFORMATION: N-terminal nitrogen is succinyl substituted; C-terminal carboxy group is replaced with a carboxyoxalyl group.

SEQ ID NO: 4  
 SEQUENCE TYPE: Amino Acid  
 SEQUENCE LENGTH: 5 amino acids  
 TOPOLOGY: linear  
 TYPE OF MOLECULE SEQUENCED: peptide or protein  
 SEQUENCE DESCRIPTION:

His-Pro-Phe-His-Leu

OTHER INFORMATION: N-terminal nitrogen is t-butyloxycarbonyl substituted; C-terminal carboxy group is replaced with a 2-pyridinylcarbamoyloxalyl group.

SEQ ID NO: 5  
 SEQUENCE TYPE: Amino Acid  
 SEQUENCE LENGTH: 4 amino acids  
 TOPOLOGY: linear  
 TYPE OF MOLECULE SEQUENCED: peptide or protein  
 SEQUENCE DESCRIPTION:

bAla-Tyr-Nva-Xaa

OTHER INFORMATION: Tyr a position 2 is O-methylated; Xaa at position 4 is a cyclohexylalanine; C-terminal carboxy group is replaced with a isovalerylcarbamoyloxalyl group.

SEQ ID NO: 6  
 SEQUENCE TYPE: Amino Acid  
 SEQUENCE LENGTH: 4 amino acids  
 TOPOLOGY: linear  
 TYPE OF MOLECULE SEQUENCED: peptide or protein  
 SEQUENCE DESCRIPTION:

Xaa-Tyr-Nva-Xaa

OTHER INFORMATION: Xaa at position 1 is a beta-valine; Tyr at position 2 is O-methylated; Xaa at position 4 is a cyclohexylalanine; C-terminal carboxy group is replaced with a isovalerylcarbamoyloxalyl group.

SEQ ID NO: 7  
 SEQUENCE TYPE: Amino Acid  
 SEQUENCE LENGTH: 4 amino acids  
 TOPOLOGY: linear  
 TYPE OF MOLECULE SEQUENCED: peptide or protein  
 SEQUENCE DESCRIPTION:

Xaa-Tyr-His-Xaa

OTHER INFORMATION: Xaa at position 1 is a beta-valine; Tyr at position 2 is O-methylated; Xaa at position 4 is a cyclohexylalanine; C-terminal carboxy group is replaced with a isovalerylcarbamyloxalyl group.

SEQ ID NO: 8  
 SEQUENCE TYPE: Amino Acid  
 SEQUENCE LENGTH: 4 amino acids  
 TOPOLOGY: linear  
 TYPE OF MOLECULE SEQUENCED: peptide or protein  
 SEQUENCE DESCRIPTION:

bAla-Tyr-His-Xaa

OTHER INFORMATION: Tyr at position 2 is O-methylated; Xaa at position 4 is a cyclohexylalanine; C-terminal carboxy group is replaced with a isovalerylcarbamyloxalyl group.

SEQ ID NO: 9  
 SEQUENCE TYPE: Amino Acid  
 SEQUENCE LENGTH: 4 amino acids  
 TOPOLOGY: linear  
 TYPE OF MOLECULE SEQUENCED: peptide or protein  
 SEQUENCE DESCRIPTION:

Ser-Gln-Asn-Tyr

OTHER INFORMATION: C-terminal carboxyl group is replaced with a carbamyloxalyl group.

SEQ ID NO: 10  
SEQUENCE TYPE: Amino Acid  
SEQUENCE LENGTH: 4 amino acids  
TOPOLOGY: linear  
TYPE OF MOLECULE SEQUENCED: peptide or protein  
SEQUENCE DESCRIPTION:

Ser-Gln-Asn-Phe

OTHER INFORMATION: C-terminal carboxyl group is replaced with a cyclohexylmethylcarbamyloxalyl group.

SEQ ID NO: 11  
SEQUENCE TYPE: Amino Acid  
SEQUENCE LENGTH: 4 amino acids  
TOPOLOGY: linear  
TYPE OF MOLECULE SEQUENCED: peptide or protein  
SEQUENCE DESCRIPTION:

Ser-Leu-Asn-Tyr

OTHER INFORMATION: C-terminal carboxyl group is replaced with a carboxyloxalyl group.

SEQ ID NO: 12  
SEQUENCE TYPE: Amino Acid  
SEQUENCE LENGTH: 4 amino acids  
TOPOLOGY: linear  
TYPE OF MOLECULE SEQUENCED: peptide or protein  
SEQUENCE DESCRIPTION:

Ser-Leu-Asn-Phe

OTHER INFORMATION: C-terminal carboxyl group is replaced with a carboxyloxalyl group.

SEQ ID NO: 13  
SEQUENCE TYPE: Amino Acid  
SEQUENCE LENGTH: 4 amino acids  
TOPOLOGY: linear  
TYPE OF MOLECULE SEQUENCED: peptide or protein  
SEQUENCE DESCRIPTION:

Thr-Gln-Asn-Tyr

OTHER INFORMATION: C-terminal carboxyl group is replaced with a carboxyloxalyl group.

SEQ ID NO: 14  
SEQUENCE TYPE: Amino Acid  
SEQUENCE LENGTH: 4 amino acids  
TOPOLOGY: linear  
TYPE OF MOLECULE SEQUENCED: peptide or protein  
SEQUENCE DESCRIPTION:

Thr-Gln-Asn-Phe

OTHER INFORMATION: C-terminal carboxyl group is replaced with a carboxyloxalyl group.

SEQ ID NO: 15  
SEQUENCE TYPE: Amino Acid  
SEQUENCE LENGTH: 4 amino acids  
TOPOLOGY: linear  
TYPE OF MOLECULE SEQUENCED: peptide or protein  
SEQUENCE DESCRIPTION:

Thr-Gln-Asn-Met

OTHER INFORMATION: C-terminal carboxyl group is replaced with a carboxyloxalyl group.



SEQ ID NO: 16  
SEQUENCE TYPE: Amino Acid  
SEQUENCE LENGTH: 4 amino acids  
TOPOLOGY: linear  
TYPE OF MOLECULE SEQUENCED: peptide or protein  
SEQUENCE DESCRIPTION:

Ser-Gln-Asn-Met

OTHER INFORMATION: C-terminal carboxyl group is replaced with a carboxyloxalyl group.

SEQ ID NO: 17  
SEQUENCE TYPE: Amino Acid  
SEQUENCE LENGTH: 4 amino acids  
TOPOLOGY: linear  
TYPE OF MOLECULE SEQUENCED: peptide or protein  
SEQUENCE DESCRIPTION:

Ser-Leu-Asn-Met

OTHER INFORMATION: C-terminal carboxyl group is replaced with a cyclohexylmethylcarbamoyloxalyl group.

SEQ ID NO: 18  
SEQUENCE TYPE: Amino Acid  
SEQUENCE LENGTH: 4 amino acids  
TOPOLOGY: linear  
TYPE OF MOLECULE SEQUENCED: peptide or protein  
SEQUENCE DESCRIPTION:

Thr-Gln-Asn-Met

OTHER INFORMATION: C-terminal carboxyl group is replaced with a cyclohexylmethylcarbamoyloxalyl group.

SEQ ID NO: 19  
SEQUENCE TYPE: Amino Acid  
SEQUENCE LENGTH: 4 amino acids  
TOPOLOGY: linear  
TYPE OF MOLECULE SEQUENCED: peptide or protein  
SEQUENCE DESCRIPTION:

Thr-Leu-Asn-Met

OTHER INFORMATION: C-terminal carboxyl group is replaced with a cyclohexylmethylcarbamoyloxalyl group.

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Europäisches Patentamt  
European Patent Office  
Office européen des brevets



11 Publication number:

**0 417 721 A3**

12

## EUROPEAN PATENT APPLICATION

21 Application number: **90117461.5**

51 Int. Cl.<sup>5</sup>: **C07K 5/10, C07K 5/08**

22 Date of filing: **11.09.90**

30 Priority: **11.09.89 US 405491**

43 Date of publication of application:  
**20.03.91 Bulletin 91/12**

84 Designated Contracting States:  
**AT BE CH DE DK ES FR GB GR IT LI LU NL SE**

98 Date of deferred publication of the search report:  
**08.01.92 Bulletin 92/02**

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54 **Novel peptidase and isomerase inhibitors.**

57 This invention relates to activated electrophilic ketone analogs of certain peptidase substrates which are useful in inhibiting serine-, carboxylic acid- and metallo- proteolytic enzymes, the inhibition of which will have useful physiological consequences in a variety of disease states.

**EP 0 417 721 A3**



European Patent  
Office

## EUROPEAN SEARCH REPORT

Application Number

EP 90 11 7461

DOCUMENTS CONSIDERED TO BE RELEVANT			
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. CL.5)
X	EP-A-0 195 212 (MERRELL DOW PHARM. INC.) 24 September 1986	7, 12, 14, 22, 24, 28, 42	C07K5/10 C07K5/08 C07K5/06 C07K5/02 C07K7/06
A	* the whole document *	1-49	C07C271/22 C07C237/22 A61K31/195 A61K37/64
A	EP-A-0 249 349 (ICI AMERICAS INC.) 16 December 1987 * the whole document *	1-49	
			TECHNICAL FIELDS SEARCHED (Int. CL.5)
			C07K C07C A61K
The present search report has been drawn up for all claims			
Place of search THE HAGUE		Date of completion of the search 14 NOVEMBER 1991	Examiner GROENENDIJK M.S.M.
CATEGORY OF CITED DOCUMENTS			
X : particularly relevant if taken alone Y : particularly relevant if combined with another document of the same category A : technological background O : non-written disclosure P : intermediate document		T : theory or principle underlying the invention E : earlier patent document, but published on, or after the filing date D : document cited in the application L : document cited for other reasons & : member of the same patent family, corresponding document	

EPO FORM 1503 01.92 (P0401)